TAMPEREEN TEKNILLINEN YLIOPISTO
TAMPERE UNIVERSITY OF TECHNOLOGY

TOMI ROSHOLM

THE PETASIS-BORONO MANNICH REACTION IN GLYCEROL

Master of Science Thesis

Examiners:
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Examiners and topic approved by the Faculty Council of the Faculty of Engineering Sciences on 7th of May 2014

ABSTRACT

TAMPERE UNIVERSITY OF TECHNOLOGY
Master's Degree Programme in Materials Engineering
ROSHOLM, TOMI: Petasis-Borono Mannich Reaction in Glycerol
Master of Science Thesis, 70 pages, 27 Appendix pages
June 2014
Major: Material Chemistry
Examiners: Professor Robert Franzén, University Lecturer Nuno R. Candeias
Keywords: Petasis-Borono Mannich reaction, glycerol, multicomponent reaction, organoboron reagents, green solvent

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The Petasis-Borono Mannich (PBM) multicomponent reaction between an amine, aldehyde and vinyl- or arylboronic acid is a highly versatile chemical reaction which can be used in the preparation of large libraries of organic compounds using differently substituted starting materials. These substrates are readily available and the reaction can be run in mild conditions in a number of organic solvents including water. Organoboron acids are in addition stable, non-toxic and environmentally friendly.

The rapid development of biodiesel industry is generating a tremendous amount of crude glycerol as a by-product and new findings for its use are highly desirable. Glycerol has been found to be an interesting green reaction medium in organic synthesis, both with and without the help of a catalyst. In some cases, the use of glycerol as a solvent has enhanced the effectiveness and selectivity of the reactions and allowed easy product separation and catalyst recycling.

The theory section of this Thesis is divided into two parts. First the details of the Petasis-Borono Mannich multicomponent reaction are explored and the mechanistic considerations of the reaction are discussed. In the second part the use of glycerol as a green solvent in organic synthesis is explored and some organic reactions where it has been found to be a successful or even beneficial reaction medium are highlighted.

The aim of this Thesis was to study the viability of using glycerol as a green reaction medium for the Petasis-Borono Mannich reaction. The reaction was studied with a variety of substituted arylboronic acids, salicylaldehydes and secondary amines using glycerol as the solvent. The PBM reaction was used in the preparation of 2H-chromene compound and the reaction was also tested in crude glycerol acquired from biodiesel production.

No general enhancement of the reaction performance was observed compared to other solvents mentioned in the literature. The outcome of the reaction was highly dependent on the activating nature of the substituents in the arylboronic acid with aryl activating groups giving products in good to very good yields while deactivating groups and steric effects dropped the yields noticeably. The yields could be improved by raising the reaction temperature. A number of secondary amines were found to be successful in the reaction whereas indoline outperformed the others, while substituents in the salicylaldehyde decreased the yields slightly.

It was shown that glycerol promoted the 2*H*-chromene formation better than water giving the product in excellent 94 % yield. The use of crude instead of pure glycerol was found to offer no promoting effects in the PBM reaction and gave the product in slightly lower yield compared to pure glycerol. However, the yield was still high enough (84 %) to warrant more research into using crude glycerol as the reaction medium for the PBM reaction.

Thus, based on results gained in this thesis, glycerol can be used as a sustainable solvent for the Petasis-Borono Mannich reaction giving comparable results to other solvent systems reported in the literature. This extends the solvent library for this useful multicomponent reaction and also further promotes the utilisation of glycerol as a sustainable reaction medium for organic synthesis.

TIIVISTELMÄ

TAMPEREEN TEKNILLINEN YLIOPISTO
Materiaalitekniikan koulutusohjelma
ROSHOLM, TOMI: Petasis-Borono Mannich –reaktio glyserolissa.
Diplomityö, 70 sivua, 27 liitesivua
Kesäkuu 2014
Pääaine: Materiaalikemia
Tarkastajat: Professori Robert Franzén, Yliopiston Lehtori Nuno R. Candeias
Avainsanat: Petasis-Borono Mannich –reaktio, glyseroli,
multikomponenttireaktio, organoboroyhdisteet, ympäristöystävällinen liuotin

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Petasis-Borono Mannich (PBM) -monikomponenttireaktio on hyvin monipuolinen amiinin, aldehydin ja vinyyli- tai aryyliboorihapon välinen kemiallinen reaktio, jonka tuotteena muodostuu muun muassa erilaisia typpiyhdisteitä, kuten aminohappoja, aminoalkoholeja ja alkyyliaminofenoleja.

PBM-reaktion etu liittyy boorihapon reaktiivisuuteen. Boorihappo on inaktiivinen aldehydiyhdisteitä kohtaan mutta reagoi vapaasti amiinin ja aldehydin muodostaman iminiumvälitilan kanssa minimoiden sivutuotteiden muodostumisen reaktion aikana. Hyödyntämällä substituoituja lähtöaineita, voidaan menetelmällä valmistaa laajoja molekyylikirjastoja nopeasti ja vaivattomasti.

PBM-reaktion lähtöaineet ovat helposti saatavilla ja reaktiossa käytettävät organobooriyhdisteet ovat stabiileja, myrkyttömiä ja ympäristöystävällisiä. Reaktion on todettu toimivan useassa eri liuottimessa, myös vedessä, tehden PBM-reaktiosta hyvin käyttökelpoisen työkalun vihreän kemian tarpeisiin.

Biodieselin tuotanto on kasvanut räjähdysmäisesti viimeisen vuosikymmenen aikana ja tämän prosessin sivutuotteena syntyy huomattavia määriä raakaglyserolia, jonka hyötykäyttö on ollut tähän mennessä rajallista sen sisältämien epäpuhtauksien takia. Lisäksi raakaglyserolin jalostus ei ole aina taloudellisesti kannattava prosessi. Uusien sovelluskohteiden kehittäminen raakaglyserolille olisikin ensiluokkaisen tärkeää, jotta biodieselistä saataisiin taloudellinen ja kestävä vaihtoehto fossiilisille polttoaineille.

Yksi viimeaikaisista uusista käyttökohteista on glyserolin käyttö liuottimena kemiallisessa syntetiikassa. Glyseroli on mielenkiintoinen vaihtoehto sen fysikaalisten ja kemiallisten ominaisuuksien ansioista, joissa yhdistyvät veden ja ionisten nesteiden hyödylliset ominaisuudet, kuten alhainen höyrynpaine, korkea kiehumispiste, biohajoavuus, myrkyttömyys, palamattomuus ja hyvät liuotusominaisuudet. Glyserolin on havaittu joissain tapauksissa mahdollistavan tuotteiden valmistuksen hyvällä saannolla ja selektiivisyydellä ja tietyissä tapauksissa toimivan myös katalyyttinä. Raakaglyserolin käytöstä liuottimena on raportoitu hyvin vähän.

Tämän diplomityön teoriaosassa esitellään aluksi Petasis-Borono Mannich -reaktiota, sen reaktiomekanismia sekä reaktio-olosuhteiden ja käytettävien lähtöaineiden vaikutusta reaktion kulkuun. Mainitaan, miten kyseiseen reaktiomekanismiin on päädytty käytännön kokeiden lisäksi käyttämällä apuna laskennallisen kemian,

erityisesti tiheysfunktionaaliteorian (DFT), keinoja. Lisäksi esitellään tiivistetysti erilaisten orgaanisten yhdisteryhmien, erityisesti typpiyhdisteiden, valmistusta PBM -reaktiolla ja minkälaisia johtopäätöksiä saaduista tuloksista voidaan vetää koskien tiettyjen liuottimien ja lähtöaineiden soveltuvuutta tähän reaktioon.

Teoriaosan toisessa osiossa käsitellään glyserolia, sen tuotantoa, käyttökohteita, ominaisuuksia ja käyttöä liuottimena kemiallisessa syntetiikassa. Erityisesti kiinnitetään huomiota sen ominaisuuksiin, rajoituksiin ja käytön ympäristöystävällisyyteen sekä esimerkkireaktioihin, joissa glyserolin on havaittu toimivan muita orgaanisia liuottimia paremmin.

Diplomityön kokeellisessa osiossa on tutkittu glyserolin soveltuvuutta Petasis-Borono Mannich -reaktion liuottimeksi valmistamalla erilaisia alkyyliaminofenoleja substituoiduista salisyylialdehydeistä, aryyliboorihapoista ja sekundäärisistä amiineista ja verrattu saatuja tuloksia kirjallisuudesta löydettyihin vastaaviin tuloksiin eri liuottimissa. Lisäksi substituenttien vaikutusta reaktion kulkuun tutkittiin ja sitä miten PBM-reaktiolle ehdotettua reaktiomekanismia voidaan käyttää näiden tulosten perusteluun. Suurin osa tutkimuksista suoritettiin kaupallisesti saatavassa glyserolissa mutta myös teollisuudesta saatu raakaglyserolinäyte osoitettiin soveltuvaksi reaktioliuottimeksi. Lisäksi PBM-reaktiota käytettiin biologisesti merkittävän rakenteen, 2*H*-kromeenin, valmistuksessa.

Tehtyjen tutkimusten perusteella glyserolia voidaan käyttää ympäristöystävällisenä liuottimena Petasis-Borono Mannich reaktiossa, vaikkakaan selvää etua saannoissa tai reaktioajoissa verrattuna muihin liuottimiin ei havaittu. Reaktion lopputulos riippui selvästi aryyliboorihapon substituenttien luonteesta. Aryyliboorihapon *para*-asemassa olevat elektroneja luovuttavat ryhmät, kuten 4-metoksi- ja 4-tolyyliryhmä nostivat saantoja verrattuna ei-substituoituun fenyyliboorihappoon, kun taas elektroneja puoleensavetävät ryhmät laskivat saantoja huomattavasti. Steerisiä esteitä aiheuttavat funktionaaliset ryhmät alensivat myös saantoja. Reaktiolämpötilaa nostamalla saatiin paremmat saannot.

Erilaisten sekundääristen amiinien havaittiin toimivan PBM-reaktiossa kohtalaisen hyvin ja erityisesti indoliinin kanssa saannot olivat yli 90 %. Kirjallisuudesta ei löytynyt aikaisempaa mainintaa indoliinin, sen johdannaisten tai *N*-alkyylianiliinien käytöstä tässä reaktiossa. Todettiin myös että tutkitut 5-metoksi- ja 4-nitroryhmät salisyylialdehydissä laskivat saantoja verrattuna substituoimattomaan salisyylialdehydiin. 2*H*-kromeeniyhdisteen valmistus onnistui erinomaisella 94 % saannolla ja glyserolin havaittiinkin toimivan tässä reaktiossa vettä paremmin. Raakaglyserolissa suoritetun PBM-reaktion saanto huononi puhtaaseen glyseroliin verrattuna noin 10 % mutta tuotetta saatiin kuitenkin hyvällä 84 % saannolla.

PREFACE

The experimental part of this Thesis was done in the synthesis laboratory of the Department of Chemistry and Bioengineering in Tampere University of Technology during January-April 2014. I want to thank my examiner professor Robert Franzén for offering me this opportunity to work in the field of organic synthesis. I'm also thankful for my second instructor university lecturer Nuno R. Candeias for the many practical advices and flexibility during the experimental work. I want to thank my fiancée Rachel for being supportive and understanding during the long hours in the lab and during this writing process. Finally, I want to thank my family and friends for all the support during my studies.

Tampere 13.04.2014

Tomi Rosholm

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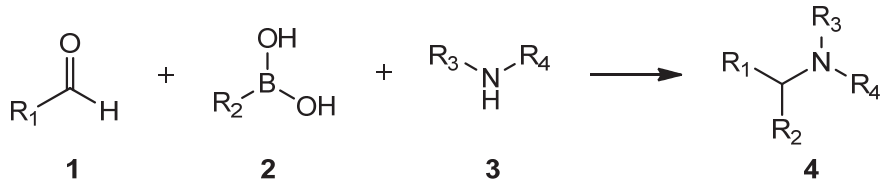
ABBREVIATIONS AND NOTATION

[bmim]BF_4	1-butyl-3-methylimidazolium tetrafluoroborate
^{13}C	carbon-13
^{1}H	proton
Ac	acetyl group
Ar	aryl group
Bn	benzyl group
br	broad (NMR)
δ	chemical shift, ppm (NMR)
d	doublet (NMR)
DCM	dichloromethane
DFT	density functional theory
DMF	dimethylformamide
DMSO	dimethylsulfoxide
EDG	electron donating functional group
eq	molar equivalent
EtOAc	ethylacetate
EtOH	ethanol
EWG	electron withdrawing functional group
Hex	*n*-hexane
HFIP	hexafluoro-*iso*-propanol
J	coupling constant (NMR)
m	multiplet (NMR)
MCR	multicomponent reaction
Me	methyl group
MeO	methoxy group
MeOH	methanol
MW	microwave
NMR	nuclear magnetic resonance
PBM	Petasis-Borono Mannich
Ph	phenyl group
rt	room temperature
s	singlet (NMR)
t	triplet (NMR)
TLC	thin layer chromatography
wt%	weight percent

1. INTRODUCTION

The Petasis-Borono Mannich (PBM) multicomponent reaction between an aldehyde **1**, aryl- or vinylboronic acid **2** and amine **3** is a highly versatile chemical reaction which can be used in the preparation of large libraries of organic compounds **4** by the simple modification of substituents in the starting materials. These starting materials are usually readily available. Among the possible reaction products are *N*-heterocycles, amino acids, amino alcohols and alkylaminophenols.



Scheme 1. *The general reaction scheme for the Petasis-Borono Mannich reaction.*

The rapid development of biodiesel industry is generating a tremendous amount of crude glycerol as a by-product which is now in desperate need of chemical utilisation. [1] Due to its easy availability along with its unique combination of physical and chemical properties which combine the advantages of water and ionic liquids, glycerol has been found to be an interesting green reaction medium for organic synthesis, both with and without the help of a catalyst. In some cases, the use of glycerol as a solvent has been found to enhance the effectiveness and selectivity of the reactions and allowed easy product separation and catalyst recycling. [1; 2]

The PBM reaction has been reported in a number of solvents such as dichloromethane (DCM), toluene, ethanol and water. [3 - 5] However, the use of glycerol as a sustainable reaction medium for this chemical transformation has not been presented. The use of glycerol as solvent could have favorable effects on the reaction outcome enhancing the rate, selectivity and yield of the reaction. Using glycerol as the solvent for the PBM reaction would also be a small contribution to the efforts of finding more uses for this by-product of biodiesel production and to, in part, help to establish the role of glycerol as one of the more sustainable solvent alternatives for organic synthesis. That is the motif for this thesis.

The literature survey of this thesis is divided into two main sections: Chapter 2 contains discussion of the Petasis-Borono Mannich reaction, its reaction mechanism and the effects of solvent, reaction conditions and used starting materials for the outcome of the reaction. Also included is a short introduction to the different compound families that can be produced with the PBM reaction. Chapter 3 focuses on glycerol and especially

on its use as a green reaction medium for organic synthesis. Its production, solvent properties, benefits and drawback are also discussed and reaction examples where it has been found to be a beneficial reaction medium are presented.

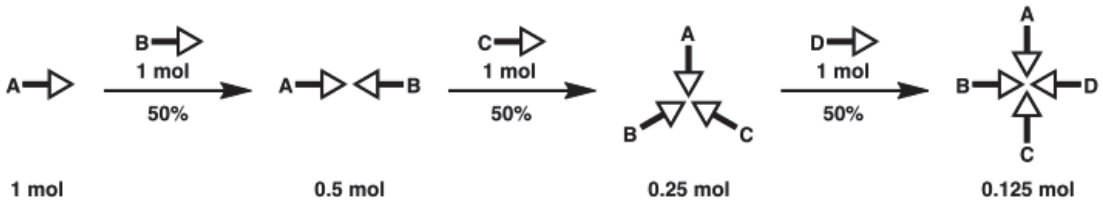
The experimental part is divided into two sections: In chapter 4 the results of the syntheses performed during this work are presented and discussed. Possible trends in reactivity between different amines, substituted salicylaldehydes and arylboronic acids and how they could be explained in terms of the proposed reaction mechanism are discussed. In addition the results obtained in glycerol are compared to reports found in the literature for other solvents in order to find out if glycerol has any enhancing effects on the reaction performance. The general synthetic method and detailed description of the syntheses and workup procedures of every product are collected to chapter 6 along with the structural data acquired by NMR spectroscopy. Chapter 5 contains the conclusions.

2. THE PETASIS-BORONO MANNICH REACTION

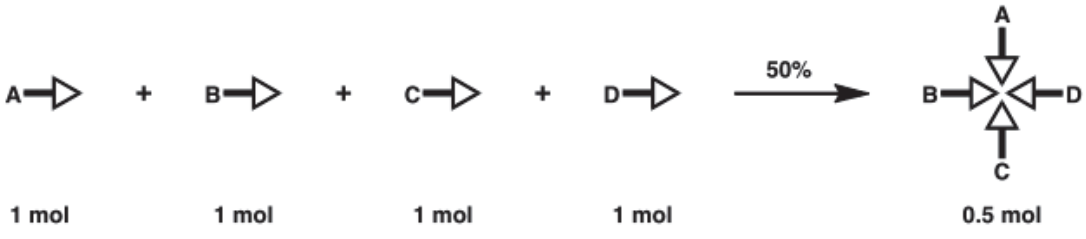
The length of a synthesis is depended upon the average molecular complexity produced in a single chemical operation and with the emergence of molecular biology and high-throughput biological screening, the demand on the number and the quality of compounds for drug discovery has increased enormously. [6]

Multicomponent reactions (MCRs) in which three or more reactants are combined in a single step to produce an array of multifunctional molecules have become an active area of research in academia and industry alike. The complexity of these molecules can be altered by the numerous possibilities in substituents in the starting materials and by various reagent combinations resulting in a high exploratory power of these reactions.

Whereas linear synthesis requires significant amounts of time and money to obtain complex target molecules, MCRs offer an access to a large library of novel and diverse structures in one single step with lower production and environmental costs due to high convergence and greater atom economy. [6]



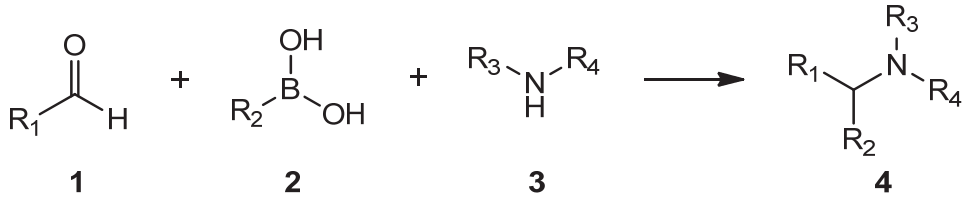
Scheme 2. *The general reaction scheme for linear synthesis. [7]*



Scheme 3. *The General reaction scheme for multicomponent reaction. [7]*

In 1993 Petasis e*t al*. [8] presented a new kind of Mannich reaction between an amine **1**, an aldehyde **3** and an organoboronic acid **2** which has developed over the last few years into a powerful synthetic tool for organic chemists. This Petasis-Borono

Mannich (PBM) reaction has been extended among other methods to solid phase, palladium-catalysed processes and tandem processes. [9] The general protocol for the PBM reaction involves stirring of the starting materials at room temperature in solvent such as dichloromethane (DCM), toluene, ethanol or even water for periods of 24 h, although sometimes the use of higher temperatures or longer reaction times is needed. However, other methods and reaction conditions such as the use of ionic liquids or microwave activation have also been designed to facilitate either a better conversion or shorter reaction times. [10; 11]



Scheme 4. *The general reaction scheme of the Petasis-Borono Mannich reaction.*

The PBM reaction is categorized to be of type II MCR which involves complex equilibria with many intermediates but eventually leads to the formation of the final product in one irreversible step – a C-C bond formation. These type II reactions are the most desirable in the context of organic synthesis. [12]

A major advantage of the PMB reaction is the wide availability of a large library of different organoboronic acids. As a result of their utility in many reactions such as Suzuki-Miyaura coupling [13; 14] a variety of aryl and heteroaryl boronic acids are now commercially available. Another benefit of organoboron acids is their stability in air and water as well as their non-toxicity and environmental friendliness. They also tolerate many functional groups which makes the excessive use of protective groups in the synthesis unnecessary. [6]

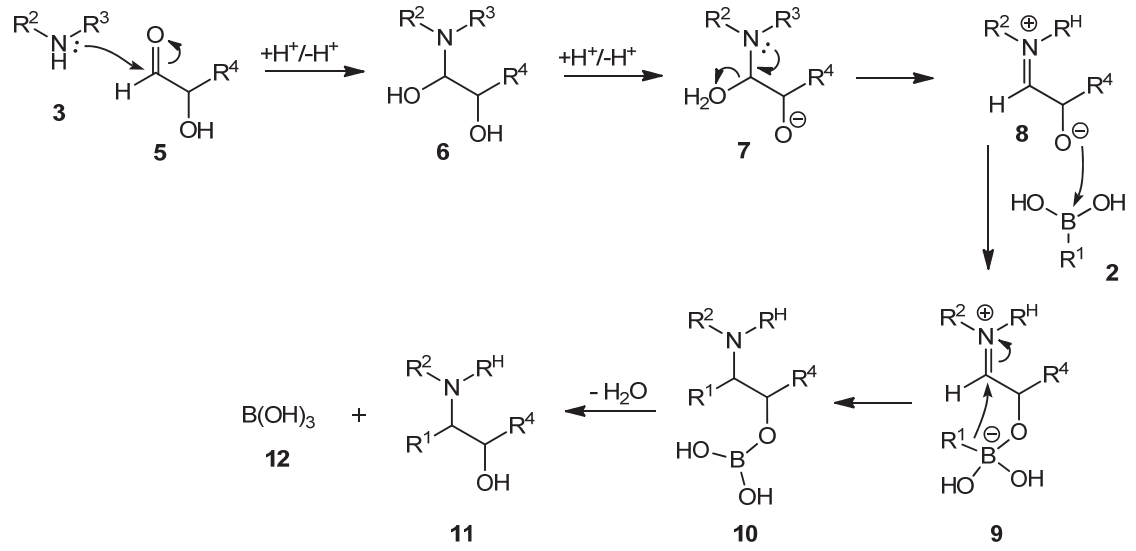
Unlike in the Mannich reaction where formaldehyde has to be used in order to prevent the undesired reaction between it and the enolate component, the success of PBM protocol is based on the fact that the boronic acid is completely inert towards the aldehyde species while it will react with the iminium or the imine bond. This lowers the probability for the formation of undesirable products and by-products.

The existence of the hydroxyl group in the α-position on the aldehyde is almost imperative for the reaction to work and most of the reports on this reaction use an aldehyde containing a hydroxyl or carboxyl group. The hydroxyl group is needed for the formation of the nucleophilic tetrahedron boronate species called the “ate complex” which promotes the transfer of the boron substituent to the imine or iminium bond. [*5*] Despite this, the use of aldehydes lacking this *α*-hydroxy group such as 2-pyridinecarbaldehyde and its derivatives has been reported. [3; 8]

2.1 Mechanistic considerations

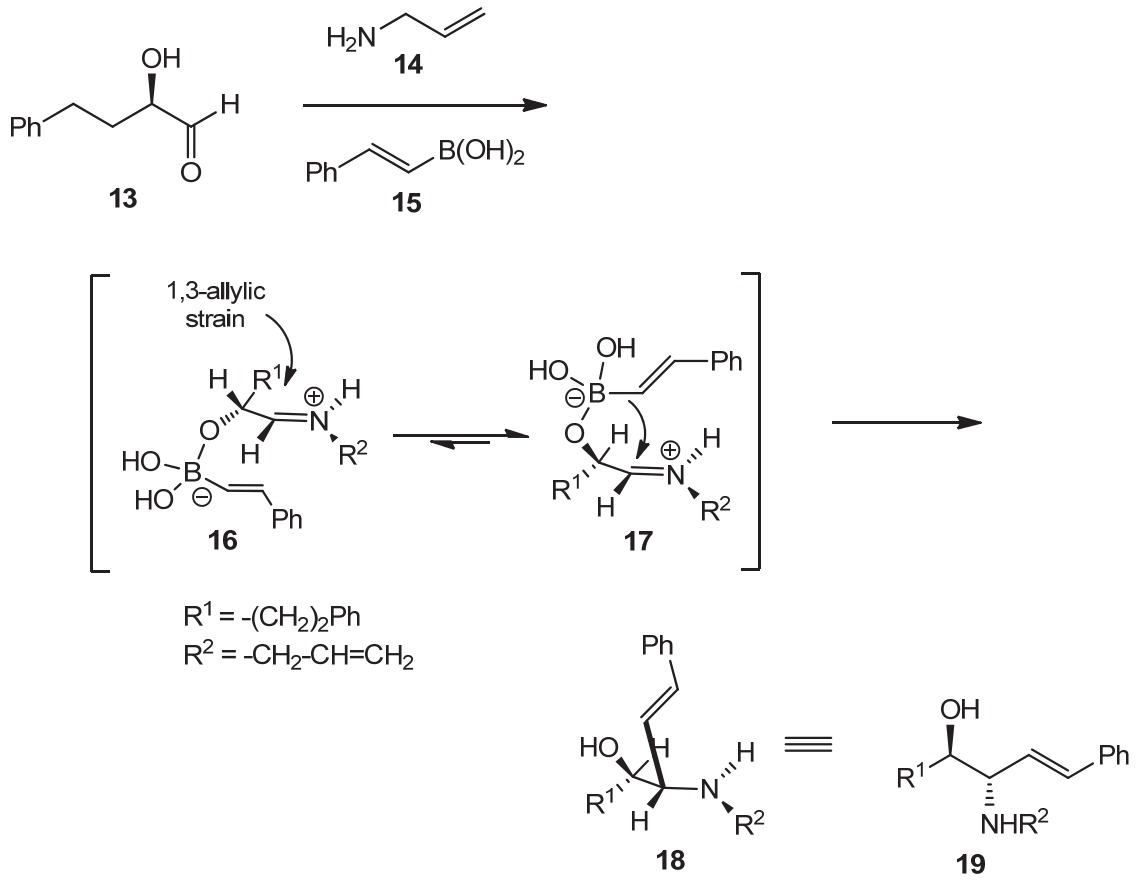
The Petasis-Borono Mannich reaction has been used to prepare several organic compounds with different functional groups and several studies based on the mechanism from these results have been presented. Density Functional Theory (DFT) calculations have also been performed and it has turned out to be a valuable tool in the elucidation of this mechanism. [15]

Tao and Li performed a theoretical study on the mechanism of the PBM reaction using DFT that suggest the following sequence of events for the use of glycoaldehyde, as shown in Scheme 5 [16]: First the amine reacts with the aldehyde in a nucleophilic addition reaction forming the carbinolamine **6** which after dehydration produces an iminium intermediate **8**. Next the boronic acids coordinates with the iminium species generating the tetrahedron "ate-complex" **9**. The C-C bond formation happens through intramolecular transfer of the aryl or alkyl group of the boronic species and finally the hydrolysis of the resulting intermediate gives the final product **11**.



Scheme 5. *The proposed mechanism for the Petasis-Borono Mannich reaction.*

The reaction with α-hydroxy aldehydes showed that the transformation described above was highly stereocontrolled. [17] When starting from racemic α-hydroxy aldehydes, the reaction formed exclusively anti-β-amino alcohol diastereomers while a single enantiomer was formed from enantiomerically pure starting materials. Pyne *et al.* suggested that with vinyl boronic acids the diastereocontrol is induced by the conformation of the "ate complex" **17** shown in scheme 6 where the 1,3-allylic strain is minimized. [18; 19]

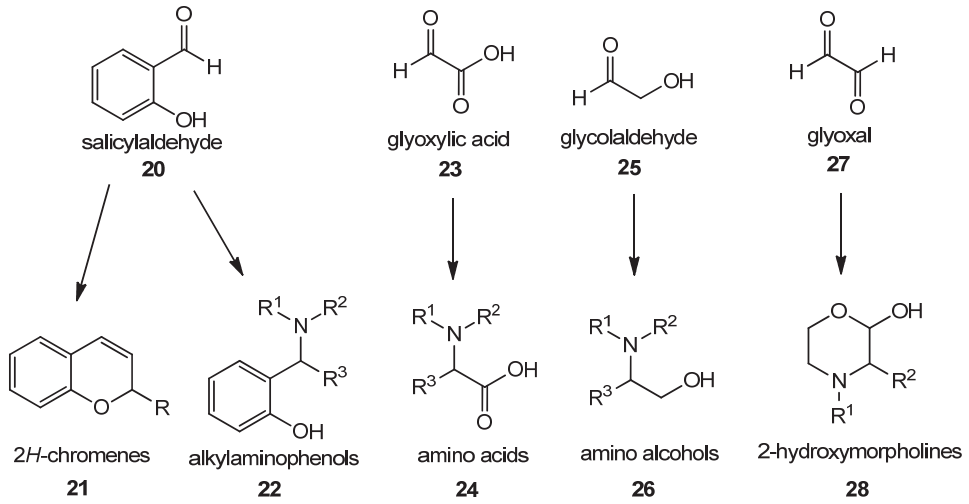


Scheme 6. *The "ate-complex" assumes a conformation **17** where the 1,3-allylic strain is minimized resulting in the formation of anti-β-amino alcohols **19**.*

For salicylaldehydes the mechanism proposed above was evaluated by DFT calculations and the experimental results were found to agree with the theoretical calculations. [20] The aryl migration from the boronic species toward the electrophilic carbon was found to be sensitive to the nature of the solvent used. Also the introduction of an electron rich methoxy substituent in the *para*-position of the aryl boronic acid was determined to lead to a more stable aryl migration transition state. This is in agreement with experimental results where the presence of this substituent in the boronic acid increased the reaction yield, when compared with its non-substituted counterpart. [20]

2.2 The PBM reaction in synthesis

Depending on the aldehyde used for the Petasis-Borono Mannich reaction, several valuable compounds can be synthesised such as α-amino acids **24**, α-amino alcohols **26**, alkylaminophenols **22**, 2*H*-chromenes **21** and 2-hydroxymorpholines **28**.

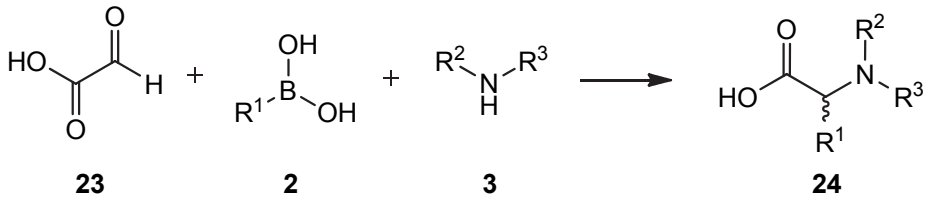


Scheme 7. *Examples of possible chemical structures accessible with the PBM reaction with different aldehydes.*

Diverse target libraries are achieved by simple addition of substituents and functional groups into the starting materials. The reaction conditions, especially the choice of solvent, have a strong effect on the outcome of the reaction. [10; 20 - 22] In the following sections some of the valuable molecules and derivatives that can be synthesised with the Petasis-Borono Mannich reaction are described.

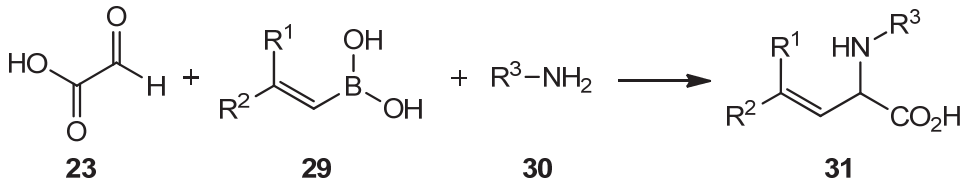
2.2.1 The preparation of amino acids

While many other methods for amino acid synthesis require the amino and carboxylic acid groups to be protected as amides, esters or other functional groups [6], the use of glyoxylic acid **23** as the aldehyde component in the Petasis-Borono Mannich reaction provides a direct one-pot method for the synthesis of unnatural amino acid derivatives **24**. [23]



Scheme 8. *The general PBM reactions scheme for amino acid synthesis **24**.*

Vinyl boronic acids **29** were used to prepare β,γ-unsaturated α-amino acids **31** in good yields at 25 – 50 °C over 12 – 48 h. Scheme 9 shows the general reaction scheme for this synthesis and table 1 shows the yields given by different substituents and solvents. [4]



23 **29** **30** **31**

Scheme 9. *The synthesis of β,γ-unsaturated α-amino acids **31**.*

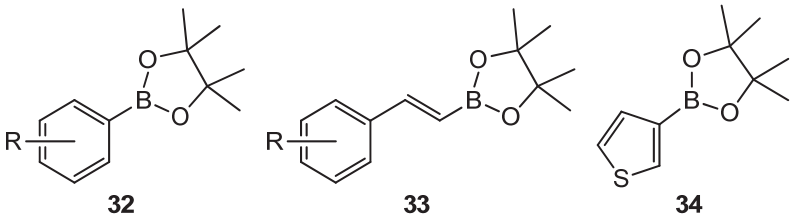
Table 1. *Reaction of glyoxylic acid with different amines and boronic acids. [4]*

Entry	R^1	R^2	R^3	Solvent	Yield (%)
1	H	Ph	$PhCH_2$	EtOH	87
2	H	Ph	Ph_2CH	toluene	94
3	H	Ph	Ph_3C	EtOH	54
4	H	Ph	$HOCH_2CH_2$	EtOH	82
5	H	Ph	$(4\text{-}MeOC_6H_4)_2CH$	toluene	92
6	H	Ph	$4\text{-}MeOC_6H_4$	EtOH	94
7	H	Ph	adamantyl	CH_2Cl_2	96
8	Br	Ph	$PhCH_2$	toluene	87
9	H	Br	$PhCH_2$	CH_2Cl_2	80

Primary, secondary and bulky amines were all reported to react under these conditions in a variety of solvents. Even water was reported to be an efficient solvent giving products with comparable yields to ethanol though higher reaction temperatures were needed (50 or 80 °C). [5]

Other boronic acids such as aryl and heterocyclic boronic acids like thienyl and pyridyl boronic acids can also be used in this reaction. [24] In fact these were found to be one of the most reactive boronic acid species for this process. When these are reacted with glyoxylic acid and amines, α-aryl glycines can be prepared and isolated in high yields by filtration followed by recrystallation or ion exchange chromatography. These are among the most important type of non-proteinogenic amino acids and act as agonists and antagonists of the glutamate receptors of the central nervous system. [25]

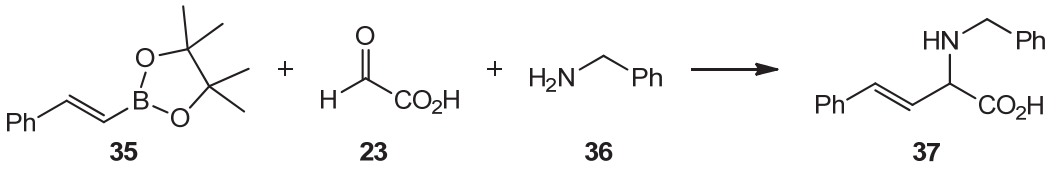
Scobie *et al.* [23] reported the use of boronic esters in the PBM reaction with glyoxylic acid. It was envisioned that chiral boronic esters could act as chiral auxiliaries which, unlike chiral centers in the aldehyde or the amine, would be eliminated from the final product during the course of the reaction. The authors used non-chiral pinacolyl boronic esters for their stability and bulkiness since these properties would be required if chiral auxiliaries were to be designed in the future.



Scheme 10. *Structures of different non-chiral pinacolyl boronic esters.*

Primary amines failed to react with glyoxylic acid and boronic esters in a range of aprotic solvents even when Lewis acid catalysts or microwave activation was used. By contrast secondary amines gave the expected products but the reactivity was strongly dependent on the nature of the boronic ester.

Late, Piettre *et al.* [21] reported that the use of protic solvents fix the reactivity issue of primary amines, yielding the desired product in 67 % yield after 72 h, as depicted below in Scheme 11. On the other hand, no reaction was observed when aprotic solvents were used and microwave activation was observed to be deleterious resulting in tarry materials.



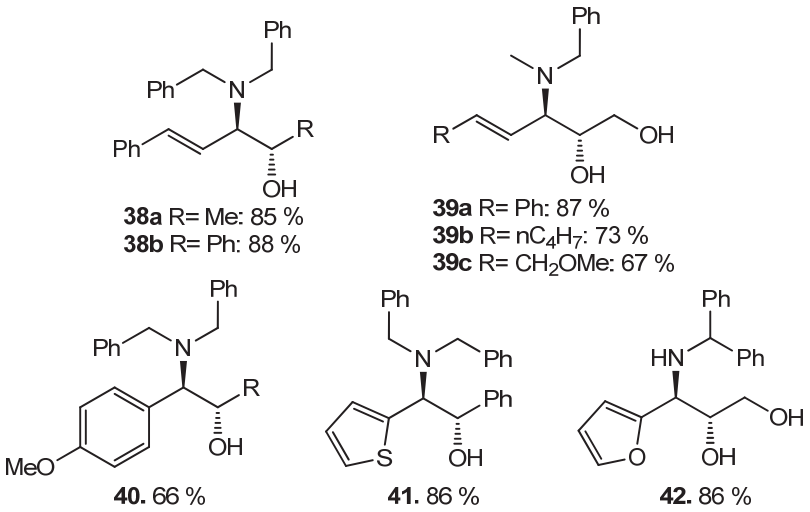
Scheme 11. *The reaction studied by Piettre et al.*

By substituting methanol with hexafluoro-*iso*-propanol (HFIP) at room temperature, the reaction time was shortened to 4 h and the yield increased to 85 %. They generated a small library of amino acids with a semi-automated synthesizer and the reaction proceeded smoothly with a variety of primary and secondary amines.

Microwave activation can be used to speed up the Petasis reaction with glyoxylic acid. [11] By irradiating the reaction mixture at 120 °C for 10 minutes it is possible to obtain the PBM reaction products in good conversions. These reaction conditions proved successful using either regular phenyl boronic acids or heteroaryl boronic acids, whilst electron poor aryl substitutents were the least reactive. The secondary amines performed best with the exception of diethylamine which only gave a moderate conversion. Hindered primary amine and *p*-anisidine also gave only moderate conversions. This study showed that microwave radiation can be used to significantly reduce the reaction time of the Petasis reaction while still achieving comparable conversions to other methods in the existing literature. [4 - 5; 23 - 24]

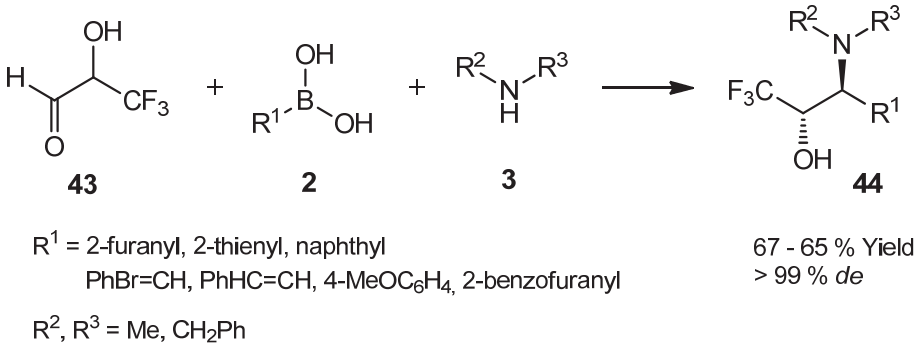
2.2.2 The preparation of amino alcohols

Among the most important uses of the PBM process is the synthesis of directly substituted vicinal amino alcohols which are common targets in natural product synthesis, drug design and asymmetric synthesis. [6] Petasis and co-workers tested glycolaldehyde derivatives as the aldehyde component in order to achieve a new synthetic route for the preparation of β-amino alcohols. The reaction was found to proceed with high levels of diastereocontrol giving exclusively the anti-isomer as the product. No racemisation was observed when optically pure α-hydroxyl aldehydes were used. [17]



Scheme 12. *The Synthesised β-amino alcohols by Petasis et al. [17]*

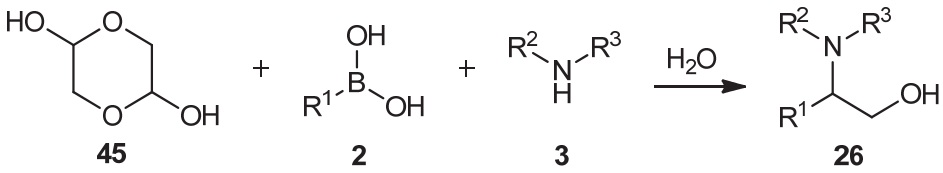
In the development of their work, Petasis and co-workers also reported a short route to anti-α-trifluoromethyl-β-amino alcohols **44** via 3,3,3-trifluorolactic aldehyde **43**.



Scheme 13. *The synthesis of anti-α-trifluoromethyl-β-amino alcohols **44**. [26]*

This methodology was also included as a key step in the synthesis of fluorinated amino acids which can be used as chemotherapeutic agents. [27]

Glycolaldehyde (dimer) **45** as the aldehyde component for the formation of α-amino alcohols **26** in water was also reported. [5]



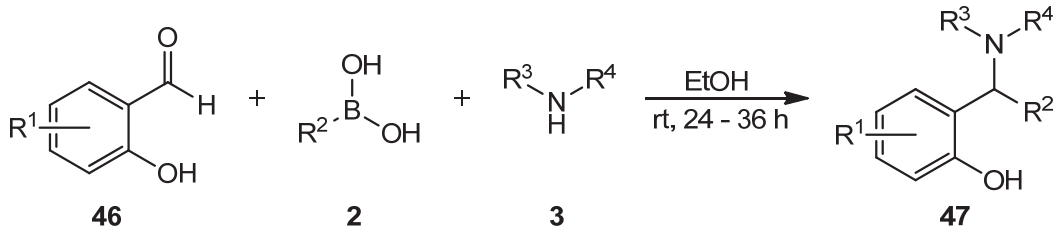
Scheme 14. *The formation of α-amino alcohols* ***26*** *in water.*

The reaction afforded products at room temperature in yields up to 69 % with *trans*-2-phenylvinylboronic acids while 1,2,3,4-tetrahydroquinoline proved to promote the reaction enough so that even phenylboronic acids could be used, affording the desired α-amino alcohols in 74-75 % yields.

2.2.3 The preparation of alkylaminophenols

Functionalized arylalkylamines and aminoalkylphenols are attractive structures for the development of pharmaceuticals and agrochemicals. [22] The use of PBM reaction with salicylaldehydes introduces a synthetic route to the more substituted derivatives of these molecules which cannot be directly accessed with the regular Mannich reaction. [28]

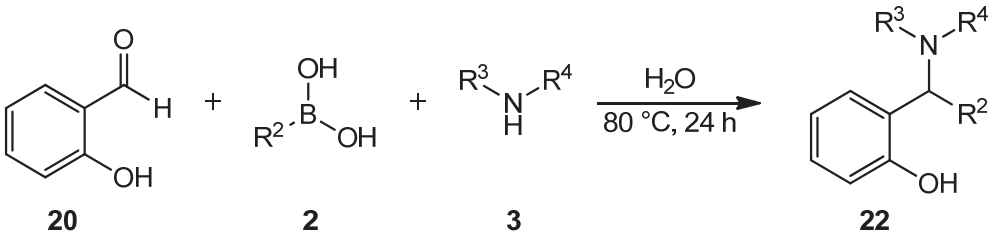
In 2000 Petasis *et al.* [22] investigated several boronic acids, amines and salicylaldehyde derivatives **46** and obtained the expected products in variable yields after 24 – 36 h at room temperature in ethanol.



Scheme 15. *The synthesis of alkylaminophenols* ***47*** *using salicylaldehydes.*

Simultaneously Wang and Finn [29] investigated the same reaction at 90 °C in dioxane. Both found out that primary amines were again quite unreactive while secondary amines gave products in better yields. The presence of *o*-hydroxy substituent in the aldehyde species was found to be imperative for the reaction to be successful. Different solvent systems were also investigated and found that polar solvents worked the best while the reaction was slower in solvents like DCM and toluene. The products could be isolated by flash column chromatography. [22]

Water can be used as the reaction medium also with salicylaldehyes. [*5*] A variety of different salicylaldehydes, amines and boronic acids were combined and the desired products were obtained in good yields after 24 h at 80 °C as shown in scheme 16 and table 2.



20 **2** **3** **22**

Scheme 16. *Alkylaminophenol synthesis in water.*

Table 2. *Alkylaminophenol synthesis in water. [5]*

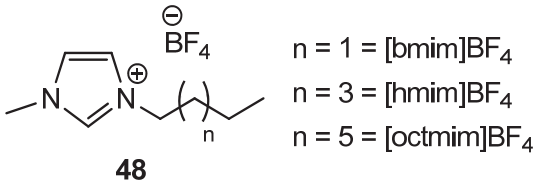
Entry	Amine	R^2	Yield (%)[a]
1	pyrrolidine	Ph	78
2	pyrrolidine	3-thiophenyl	94
3	piperidine	*p*-tolyl	96
4	piperidine	3-thiophenyl	91
5	dibenzylamine	*p*-tolyl	99
6	*N*-benzylmethylamine	4-methoxyphenyl	98
7	diallylamine	Ph	82
8	diallylamine	3-thiophenyl	96

a: Isolated yields by preparative thin-layer chromatography (hexane/EtOAc)

In fact water was found to be better solvent for this reaction than ethanol. It was observed that electron-donating groups on the boronic acid appeared to improve the reaction whereas the substituents in the aryl ring of the aldehyde had no apparent influence on the reaction. Both cyclic and acyclic secondary amines gave high yields. Especially dibenzylamine (entry 5) and diallylamine (entry 8) performed extremely well in water. When phenyl boronic acid was used, the yields ended up being slightly lower. Because of recent studies reporting on the accelerating nature of water over some reactions, the water system was compared to other organic solvents but no accelerating effect over the reaction was found.

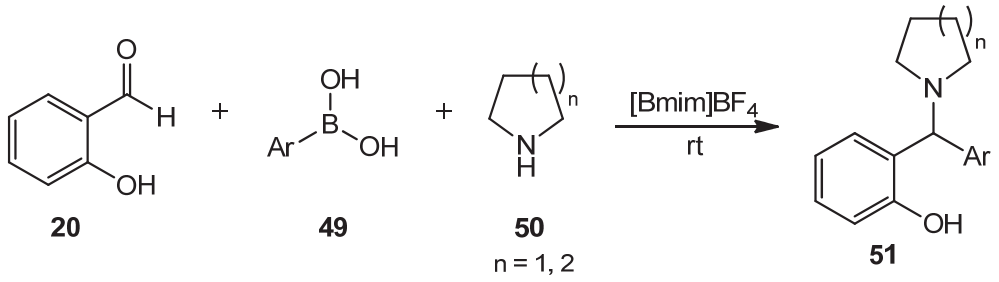
Microwave assisted protocol was also reported with reactions involving salicylaldehyde. [11] The reaction times were reduced the same way as with reactions with glyoxylic acid but only secondary amines were found to be reactive, and only the imine intermediate could be detected when testing primary amines. The desired products could be isolated by column chromatography in good yields except in the case of 2-benzofuranyl due to poor stability.

Yadav *et al.* reported in 2007 [10] on the accelerating nature of ionic liquids when used as the reaction solvent. Ionic liquids are used as green solvents and their properties such as hydrophilicity, hydrophobicity, Lewis acidity, viscosity and density can be altered by the fine-tuning of parameters such as the choice of the ions and the length of the alkyl chain attached to the cation.



Scheme 17. *The chemical structure of representative ionic liquids.*

A wide range of boronic acids and secondary amines were reacted with salicylaldehyde and its derivatives in 1-butyl-3-methylimidazolium tetrafluoroborate [bmim]BF_4 at room temperature and the desired alkylaminophenols were obtained in high yields under mild conditions. [10]



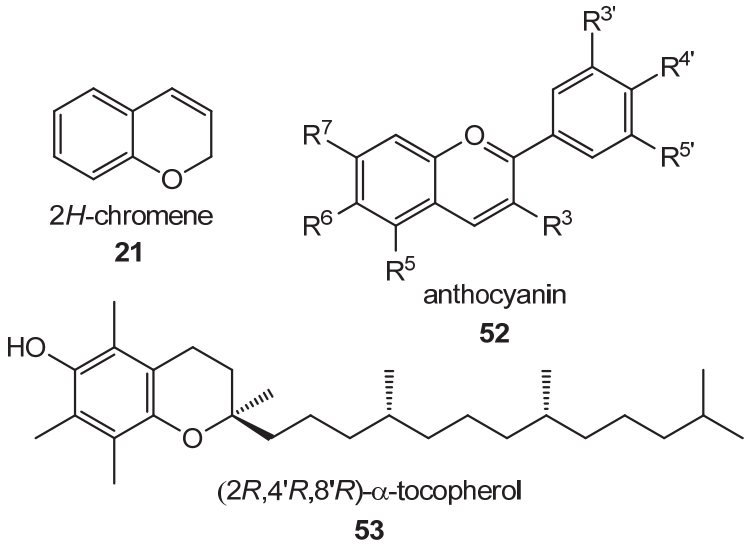
Scheme 18. *The Reaction scheme for the use of ionic liquid [bmim]BF_4 as the solvent.*

The products were easily extracted with diethyl ether and the ionic liquid was washed and reused in the successive reactions. The use of ionic liquid not only increased the yield but also reduced the reaction time. They also reported that the ionic solvent could be reused several times and even after four cycles the product could still be obtained with similar yield and purity as in the first cycle. The use of ionic liquid as solvent in this reaction helps to avoid the use of high temperatures, MW activation and long reaction times. This added to the green nature of ionic liquids makes this protocol a sustainable alternative to the synthesis of alkylaminophenols.

Limin *et al.* [30] reported in 2010 on the solvent-free synthesis of alkylaminophenols without catalysts. When optimizing the reaction conditions, the authors found out that an excellent yield was achieved at 80 °C only after 2 h while raising the temperature over 80 °C decreased the yield. Many secondary amines and boronic acids were tested and the conclusions were comparable to studies mentioned before: Aryl and heteroaryl boronic acids worked well in most cases with cyclic amines, dibenzylamine and benzylmethylamine giving good 80 – 96 % yields. The aryl boronic acids bearing an electron-donating substituent in the *para*-position in the phenyl ring gave higher yields compared to electron-withdrawing groups, in which *p*-fluorophenylboronic acid led to the lowest yield. 4-Methyl and 3,5-di-*tert*-butyl groups in the aldehyde decreased the yield slightly. This methodology was able to reduce the reaction time to 2 h without the use of microwave radiation and also improve the greenness of the reaction because no solvent was needed for the reaction to proceed.

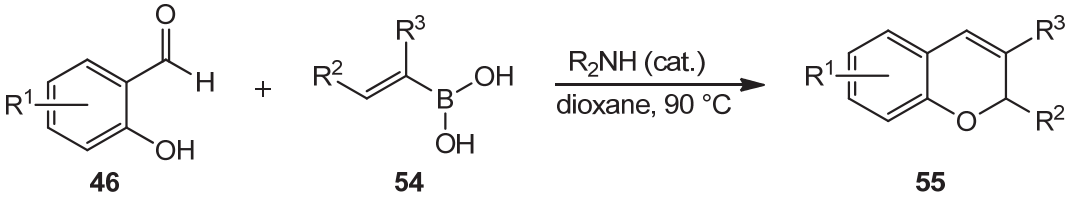
2.2.4 The preparation of 2*H*-chromenes

The 2*H*-chromene moiety **21** is a common structural feature of many biologically active molecules and is present in the structures of natural flavonoids, anthocyanins **52** as well as in the members of the vitamin E family namely tocopherols and tocotrienes. [31 - 36]



Scheme 19. *The chemical structure of 2H-chromene* ***21*** *and other natural molecules containing 2H-chromene moiety.*

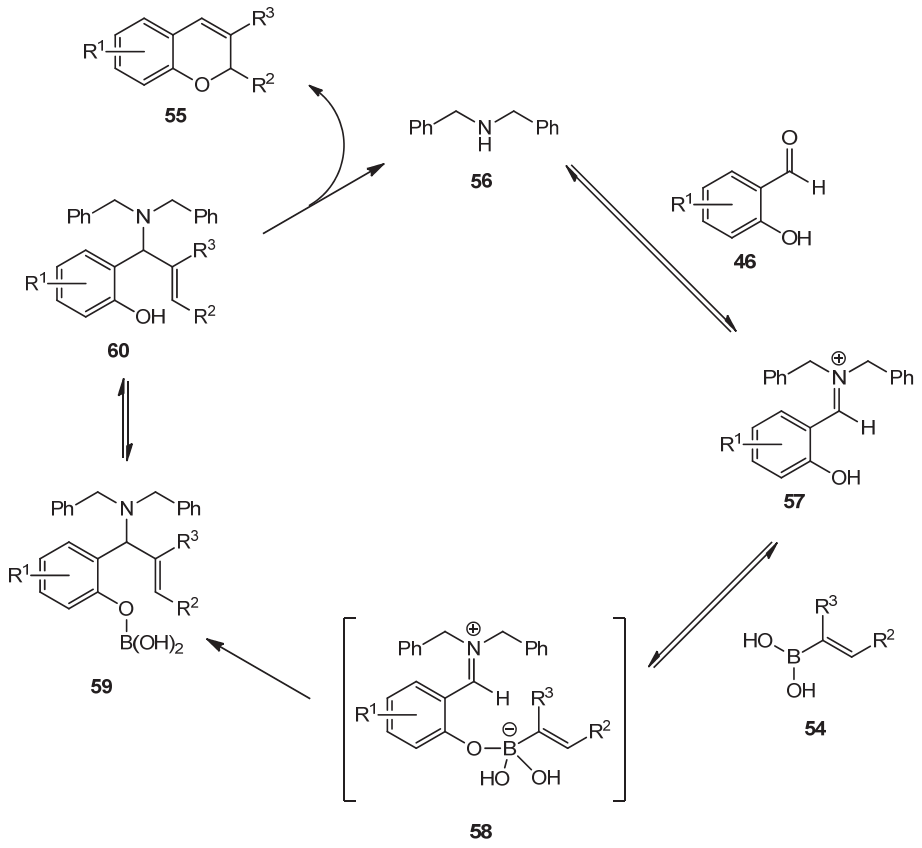
Wang and Finn observed that the Petasis products derived from salicylaldehydes and vinylboronic acids undergo cyclization to 2*H*-chromene compounds **55** with the ejection of amine upon heating.



Scheme 20. *Wang and Finn's original PBM reaction for the formation of 2H-chromenes* ***55****. [29]*

They reported that using 5 mol % of dibenzylamine **56** in dioxane at 90 °C for 12 h resulted in the product formation in excellent 92 % yield.

The proposed mechanism for this reaction is represented in Scheme 21.

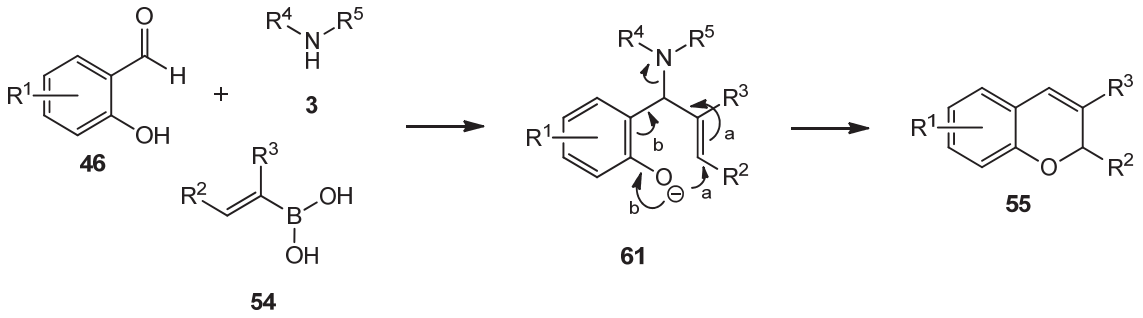


Scheme 21. *The proposed mechanism for the formation of 2H-chromenes* ***55****. [29]*

It involves the iminium ion **57** formation followed by the formation of the "ate complex" **58** just like in the regular Petasis reaction. After the intramolecular migration of the vinyl group, the boronic acid gets hydrolysed and the cyclisation step is promoted by the amine protonation, regenerating the catalytic dibenzylamine **56**.

Candeias *et al.* [20] and almost simultaneously Petasis and co-workers [31] demonstrated that this reaction could also be run in water and other protic solvents such as ethanol. However, in water stoichiometric amount of the amine was necessary to promote efficient conversion and dibenzylamine was among the most efficient amines used. It has also been reported by several groups that this chemistry works well in ionic liquids, under microwave radiation and by employing potassium trifluoroborates. [31]

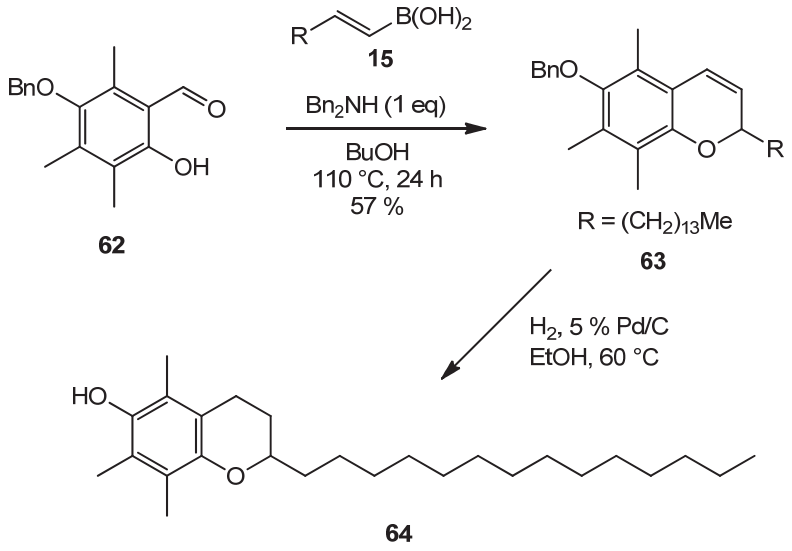
There are 2 proposed mechanisms for the formation of 2*H*-chromenes which are depicted in Scheme 22 below.



Scheme 22. *The proposed two pathways for the chromene cyclisation step. [15]*

It was proposed that the cyclisation involves either an intramolecular nucleophilic displacement of the ammonium leaving group which is the *pathway a* in the Scheme 22 above or a 6π-electrocyclisation which is represented by *pathway b*. However based on Gois and co-workers' unsuccessful experiments on trying to obtain some enantioselectivity in the chromene formation using (*S*)-α,α-diphenylprolinol as the amine component at 80 °C it was concluded that, at least in water, the reaction probably proceeds via *pathway b*. [5]

This reaction was used to synthesise among other compounds an alkyl (±)-α-tocopherol analog **64** using butanol as solvent for the Petasis step which is shown below in Scheme 23.



Scheme 23. *The synthesis of an alkyl (±)-α-tocopherol analog **64** using 2H-chromene reaction as the initial reaction step followed by catalytic hydrogenation reaction. [31]*

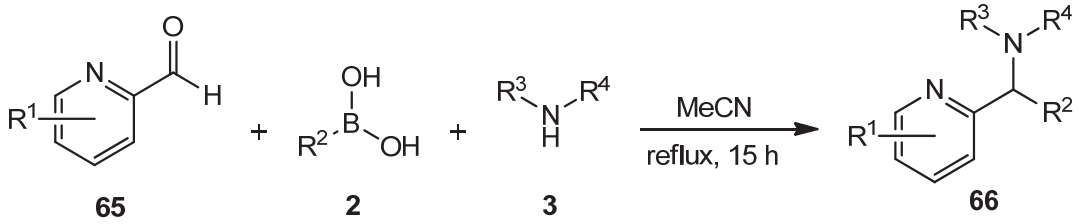
This approach presents an alternative method for the synthesis of these molecules and allows the convenient introduction of a side chain in one or two steps.

2.2.5 The reaction of 2-pyridinecarbaldehydes and its derivatives

Only a few aldehydes, that is glyoxylic acid, α-hydroxyl aldehyde and salicylaldehydes are usually employed in PBM reaction. This is because the previous studies and compu-

tational calculations performed for the PBM reaction seem to support the aforementioned mechanism for the "ate complex" which requires the α-hydroxyl group in the aldehyde species. However in 2000 Bryce and Hansen [37] reported on the use of heterocyclic aldehydes with the PBM reaction under catalyst-free conditions. These aldehydes have a heteroatom instead of the hydroxyl group alpha to the aldehyde group.

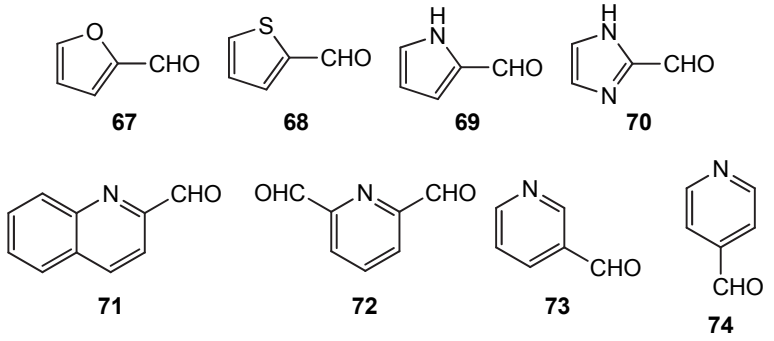
Mandai *et al.* improved on this method by exploring 2-pyridinecarbaldehydes **65** and its derivatives with various amines and boronic acids in different solvents in the absence of a catalyst. [3]



65 2 3 66

Scheme 24. *The PBM reaction with 2-carbaldehydes* ***65****.*

Solvents like DCM, dichloroethane, acetonitrile and hexafluoro-*iso*-propanol (HFIP) allowed the formation of the PBM reaction products in 55-73 % conversion. Contrastingly, solvents such as MeOH, H_2O and 1-butyl-2,3-dimethylimidazolium tetrafluoroborate ([bdmim]BF_4), which are often used in Petasis reaction, resulted only in 10 % conversion. Acetonitrile was found to clearly enhance the reaction rate even though the reason for this solvent effect is unknown. As with reactions with other aldehydes, primary amines formed products in low conversions while secondary amines after optimized reaction conditions gave products up to 96 % yield. In figure 25 are shown aldehydes found to be ineffective in the Petasis reaction.



67 68 69 70 71 72 73 74

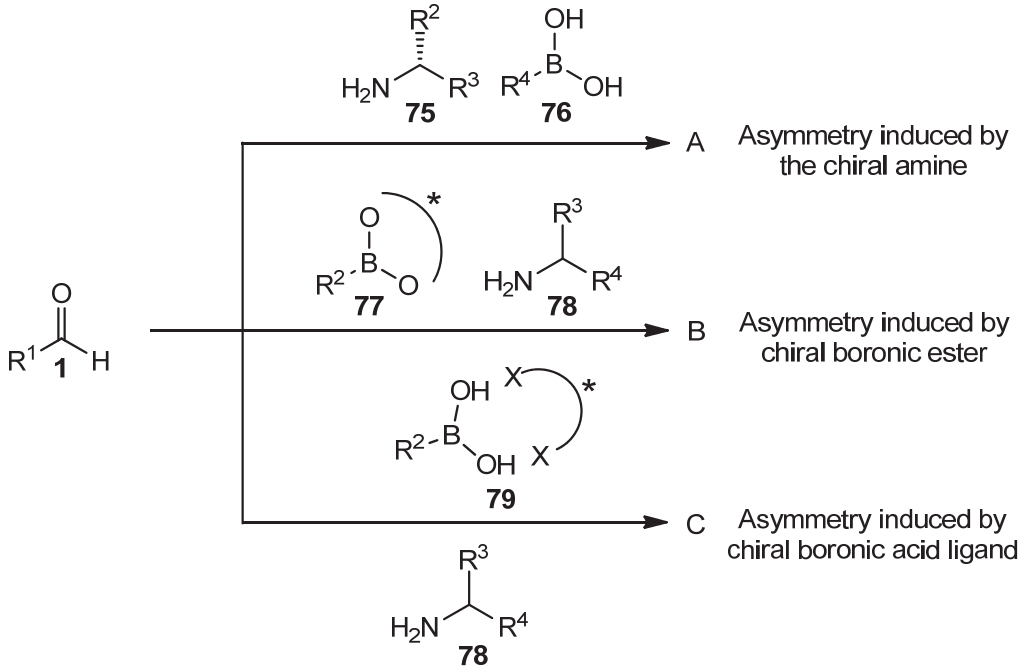
Scheme 25. *Ineffective aldehydes in the Petasis reaction. [37]*

These aldehydes, including five-membered heteroaromatic aldehydes as well as 3- and 4-pyridinecarbaldehydes resulted in the formation of a complex mixture or in the recovery of the aldehyde suggesting that the structure of the aldehyde component is essential for the reaction to proceed. It seems that the α-heteroatom in the aldehyde plays an important role in bringing the boronic acid close to the reaction site and/or in the intramo-

lecular activation of the boronic acid by the "ate-complex" formation by the nitrogen atom. These 2-substituted pyridine compounds are attractive scaffolds for biologically active compounds. [37]

2.2.6 Asymmetric Petasis-Borono Mannich reaction

The functionalisation and introduction of new asymmetric centers to molecules is of great importance in chemical synthesis. 3 different approaches have been taken in order to achieve stereocontrol in the Petasis-Borono Mannich reaction [15]: In the first case the asymmetry is driven by a stereogenic carbon in the amine **75** that can induce regioselectivity on the formation of new C-N bond. This is the pathway A in scheme 26. The second method involves the use of enantiopure or enantioenriched boronic ester **77** resulting in the formation of an enantiomerically pure side product (pathway B). In the last approach shown as pathway C, chiral ligands are complexed with the boronic esters leading to the formation of an enantioenriched product.



Scheme 26. *Different ways to induce chirality into the PBM reaction product.*

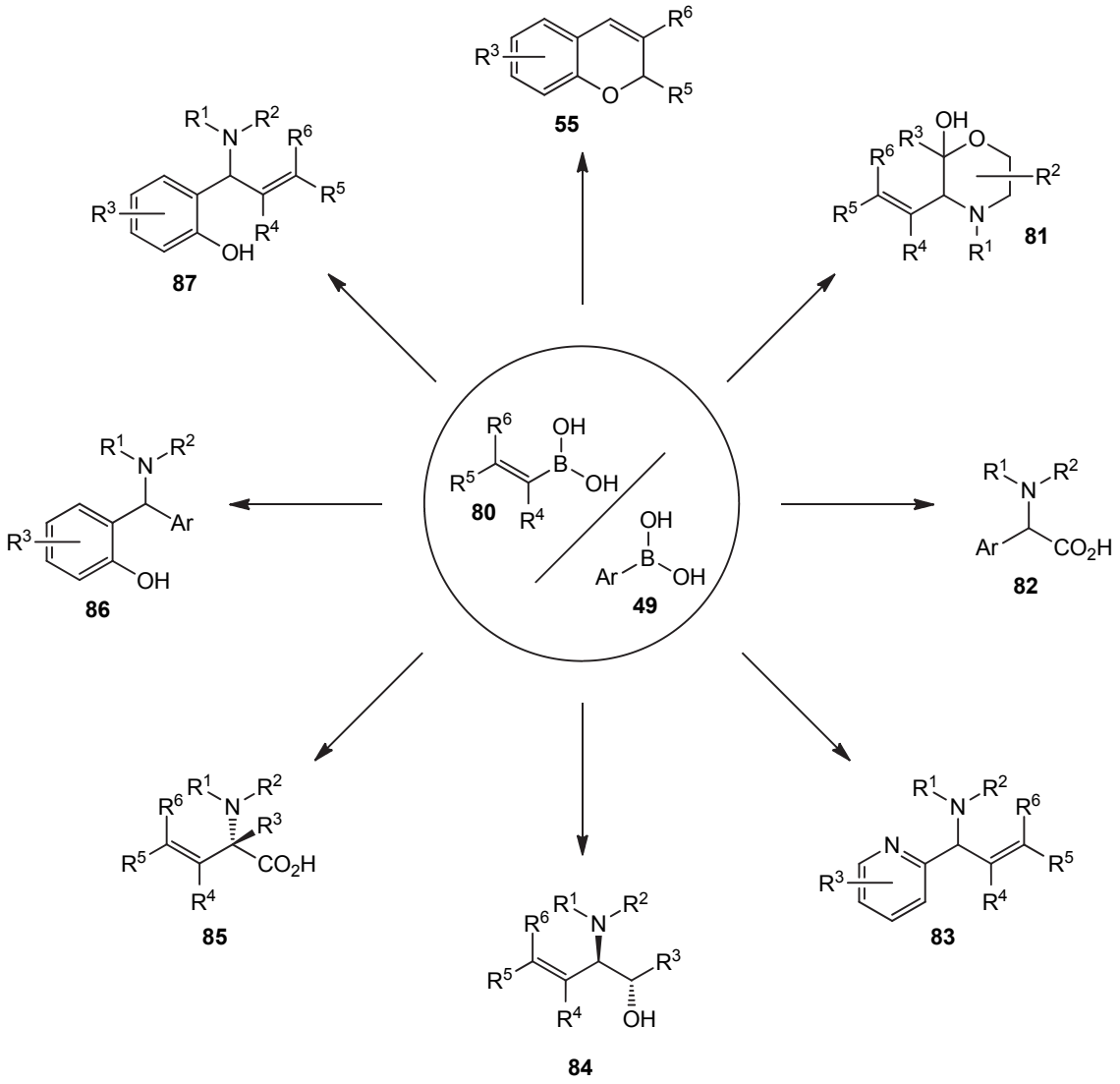
Petasis [4] and Nanda *et al.* [38] among others have reported on the use of chiral amines as a way to prepare PBM reaction products in good yields and high diastereoselectivities while Lou and Shaus [39] and in 2013 Wei-Cheng *et al.* [40] reported the use of chiral biphenols as effective catalysts for the asymmetric PBM reaction. In the report made by Wei-Cheng and co-workers, various salicylaldehydes, secondary amines and organoboronic acids were found to be suitable for this asymmetric reaction and a broad range of alkylaminophenol derivatives bearing various functional groups could be ob-

tained in moderate to good enantioselectivities by using chiral BINOL as catalyst. Despite this, no chiral catalyst for the general reaction has so far been found.

2.3 Summary

The one-step, multicomponent Petasis-Borono Mannich reaction between an amine, an aldehyde and a boronic acid derivative is a highly versatile reaction which utilizes readily available starting materials that can incorporate a variety of functional groups and complexity into the product. Based on experimental and computational studies, the reaction seems to proceed via coordination of the boronic acid with the iminium species generating the tetrahedron “ate-complex” which is followed by the intramolecular transfer of the group from the boronic acid to the iminium carbon giving the final product after hydrolysis.

In certain cases with certain chiral components, high degree of stereocontrol can be achieved allowing the synthesis of enantiomerically pure chiral molecules. The reaction tolerates many functional groups so the use of protecting group is minimized. In certain cases the reaction can be accelerated with microwave activation. The reaction products can be usually isolated from the reaction mixture by a simple filtration or liquid-liquid phase extraction. The reaction can also be run in a variety of different solvents including water and ionic liquids and it doesn’t require hazardous or toxic chemicals making it a green alternative for the production of a huge library of substituted amines such as amino acids, amino alcohols, alkylaminophenols, and many heterocycles as shown in scheme 27.



Scheme 27. *Examples of the possible chemical structures accessible with the Petasis-Borono Mannich reaction with vinyl and arylboronic acids.*

These molecules are of potential interest to the synthesis of natural molecules, drug discovery and development as well as material chemistry. [6]

3. GLYCEROL AS A GREEN SOLVENT IN ORGANIC SYNTHESIS

Taking into account the impact of chemical processes on the environment, the search for green solvents has become a great challenge in organic synthesis. As solvents are responsible for a large part of the waste and pollution generated by chemical processes, great care should be taken in choosing the most beneficial solvent not only in terms of the reaction performance but also in the greenness of that process. [41]

Most solvents employed in organic reactions today come from non-renewable fossil sources which have a negative impact on the health and on the environment. Water and biomass-derived chemicals are a promising alternative for these petrochemical-based solvents and they exhibit many advantages such as biodegradability, low vapour pressure and high boiling point which are in accordance with different international legislations pushing forward the reduction of volatile organic compounds (VOCs) in the atmosphere. [1; 42]

Due to its easy availability along with its unique combination of physical and chemical properties glycerol, also known as glycerine or propane-1,2,3-triol has recently emerged as an economically appealing and safe solvent for organic synthesis both in catalysed and non-catalysed reactions which is illustrated by the increasing number of papers that have appeared in the last few years describing such applications. [2]

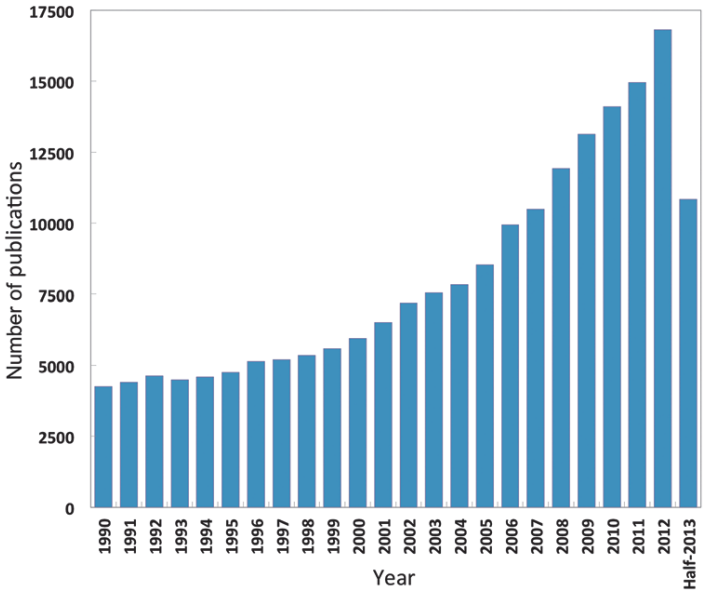
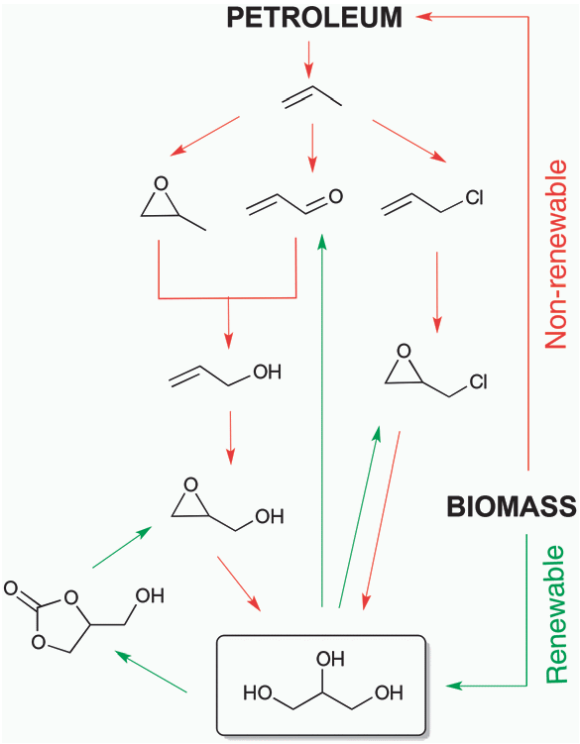


Figure 28. *The number of publications containing "glycerol" as the topic 1990 – 2013, according to a SciFinder® search. [2]*

Remarkably, in some cases, the use of glycerol as a solvent has even been found to enhance the effectiveness and selectivity of the reactions. [1]

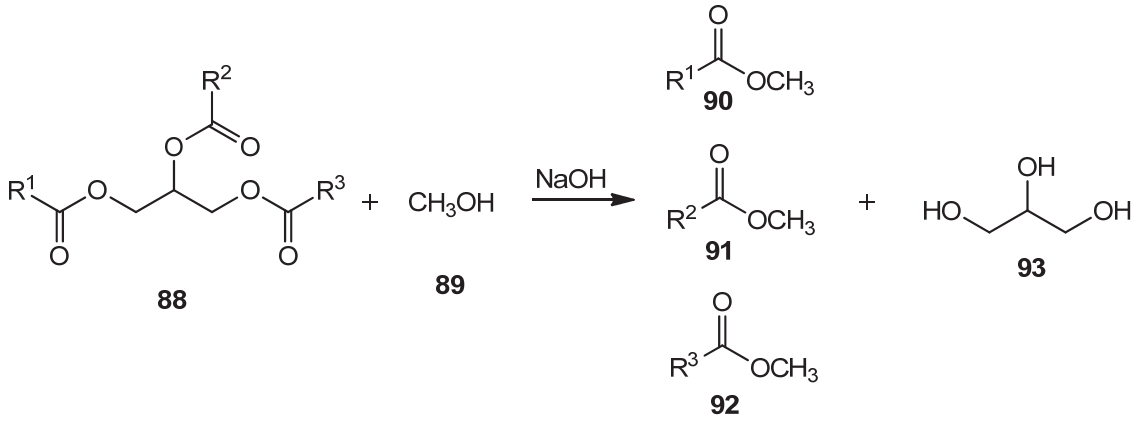
3.1 Production and applications

Glycerol is the main co-product of biodiesel and oleochemical production. Only 20 % of the world production is prepared synthetically from the chemical conversion of propylene. [43] The production routes to glycerol from either non-renewable or renewable sources are represented in scheme 29.



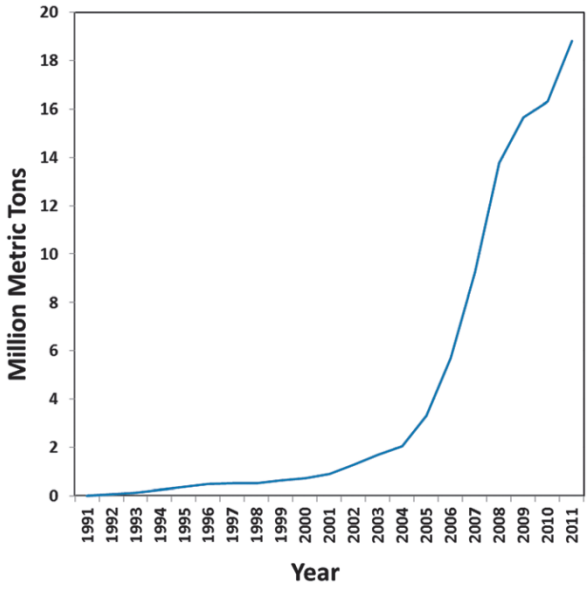
Scheme 29. *Glycerol production from renewable and non-renewable sources. Also shown are some of the valuable chemicals used in synthesis which production from non-renewable petroleum sources can be substituted with glycerol. [2]*

Glycerol is traditionally produced as a by-product of the transesterification of a triglyceride in the production of natural fatty acid derivatives such as biodiesel and represents more than two-thirds of the total glycerol output. [2; 44] In this reaction, a molecule of triglyceride **88** reacts with three molecules of methanol **89** under base catalysed conditions affording three molecules of fatty acid methyl esters **90 - 92** that is the biodiesel and a molecule of glycerol **93**.



Scheme 30. *Production of biodiesel by transesterification of triglyceride. [45]*

As a by-product of the biodiesel production glycerol represents ca. 10 wt% of the total output and its worldwide production has surpassed 2 million metric tons in 2010. [46] The production rate and demand for biodiesel are expected to grow in the near future due to the dwindling oil reserves followed by the increase in oil prices, as well as the emergence of other large-scale processes based on the conversion of cellulose and lignocelluloses in which glycerol is also a by-product. [1] Additionally, the development of the third generation feedstock for biodiesel production using microalgae or land plants unsuitable for food are expected to increase the commercial quantities of biodiesel in the upcoming years. [47; 48] Global climate change and improving energy stability have also become growing concerns throughout the world. [49] The trend in worldwide biodiesel production is shown in Scheme 31.



Scheme 31. *Biodiesel production 1991 - 2011. [46]*

Glycerol is also very cheap because in addition to the already existing huge surpluses, it is constantly being produced on a large scale in the vegetable oil industry. In 2012

the price of pharmaceutical USP grade glycerol was about 0.80 €/kg while the price of 80 % pure crude glycerol was about 0.40 €/kg [49] This impressive and fast development of the biodiesel industries has led to a large surplus of glycerol that is now in urgent need of utilisation. [1]

There are currently a high number of applications for glycerol in cosmetic, pharmaceutical and food industries. It is used as a humectant, plasticizer, emollient, thickener, dispersing medium, lubricant, sweetener, bodying agent and antifreeze among other uses. In addition, glycerol derivatives such as glycerol esters are used extensively in many industries. [2; 50]

Glycerol is also used as a raw material in different chemical syntheses. [50] The focus in this area is on the development of processes to transform glycerol into value-added chemicals which are traditionally being prepared from petrochemical sources or which production suffers from environmental problems. [1] This green approach to these small platform chemicals in which non-renewable petroleum source has been substituted by biomass-derived glycerol is represented in Scheme 29. [42] Glycerol reforming for hydrogen production and its transformation into fuel additives are also active areas of research. [1]

Although successful results of converting glycerol into other valuable chemicals have been reported in the literature, other methods for glycerol waste utilisation must also be considered. In particular, glycerol use as solvent or as a precursor for the synthesis of other biomass-based solvents in organic reactions has recently been reported as a feasible and promising approach. [42] The direct use of glycerol as a solvent offers an undeniable economically and environmentally viable application for this natural polyol.

However, in all of the above-mentioned applications, whether as a reactant, an additive or as a solvent, glycerol is principally used as a highly refined and purified product. [50] The crude glycerol acquired from transesterification process is a brown mixture in which the actual glycerol content can vary from 85 – 98 % while the other main components are small chain alcohols such as methanol, water, catalyst residual and free fatty acids, fatty acid esters or fatty acid salts. [43; 50] Thus using glycerol for example in food, cosmetics or pharmaceutical applications requires it to be purified further with bleaching, deodorizing and ion exchange to remove trace impurities and to refine it to meet the purity demands required by these industries. Purifying glycerol to that stage, however, is very costly and generally out of the range of economic feasibility for biodiesel plants. [50] As more and more crude glycerol is being produced by the biodiesel industry, economical ways to utilise this low-grade form of glycerol has to be explored to further promote biodiesel production as an economically and environmentally feasible alternative for fossil fuels.

3.2 The solvent properties of glycerol

In its pure form glycerol is a sweet-tasting, clear, colourless, odourless and viscous liquid. Being a trihydric alcohol, glycerol is a polar protic solvent with three hydroxyl groups that control its solubility.

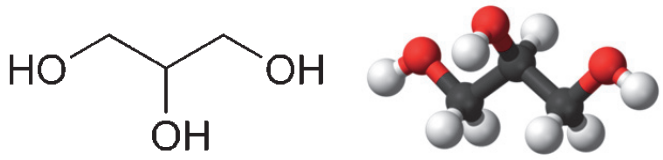


Figure 32. *Skeletal and ball and stick model of glycerol.*

Glycerol is completely soluble in water and in short chain alcohols, sparingly soluble in many common organic solvents such as ethyl acetate, dichloromethane and diethyl ether, and it is insoluble in hydrocarbons. At low temperatures (< 17.8 °C), glycerol forms crystals. Its specific density is 1.26 g/cm^3 and its molecular weight is 92.09 g/mol. [42]

Glycerol combines the advantages of water which are low toxicity, low price and wide availability and the advantages of ionic liquids such as high boiling point and low vapour pressure. These advantages make it ideal for use as a sustainable solvent in organic synthesis. [41] The properties of selected green solvents have been compared in the table 3 below

Table 3. *Comparison of the different properties of alternative green solvents. [51]*

	Glycerol	H_2O	$BmimPF_6$	C_6F_{14}
BP [°C]	290	100	>300	58-60
Vapor pressure (50 °C) [mmHg]	<1	92.51	<1	n.a
Dielectric Constant (25 °C)	42.5	78.5	11.4	<5
Viscosity (30 °C) [cP]	692	1	312	n.a
Density [g/ml]	1.29	1	1.37	1.66
Biodegradability	Yes	-	No	No
LD_{50} (Oral Rat) [mg/kg]	12,600	>90,000	~1500	~5000

Glycerol has a dielectric constant of 42.5 at 25 °C which is in-between that of water (78.5) and an ionic liquid such as 1-butyl-methylimidazolium hexafluorophosphate ([BMIm]PF6, 11.4). This in addition to its high polarity and high boiling point make glycerol a very attractive solvent for microwave (MW) assisted reactions. Microwave heating is based on the ability of a solvent to absorb microwave energy and convert it into heat at a given frequency and temperature. [43] This effect is usually enhanced when the dielectric constant of the solvent or the amount of hydroxyl groups in the solvent increases which is why MW assisted reactions with glycerol as the solvent of choice has recently been investigated. [51]

Like other polar solvents such as water, DMSO and DMF, glycerol is able to facilitate the dissolution of inorganic salts, acids, bases, enzymes and many transition metal complexes. In addition it also dissolves organic compounds that would be poorly miscible in water. Many hydrophobic solvents such as ethers and hydrocarbons are immiscible in glycerol which enables the reaction products to be removed by simple liquid-liquid phase extraction. [42]

As mentioned above, glycerol is non-volatile under normal atmospheric pressure and has a high boiling point of 290 °C. Taking advantage of this high boiling point and the thermal stability of glycerol, reactions can be performed at high temperatures allowing the acceleration of the reaction or making reactions that would not proceed in low boiling point solvents possible. [42] Moreover, these properties make distillation of the reaction products a feasible separation technique.

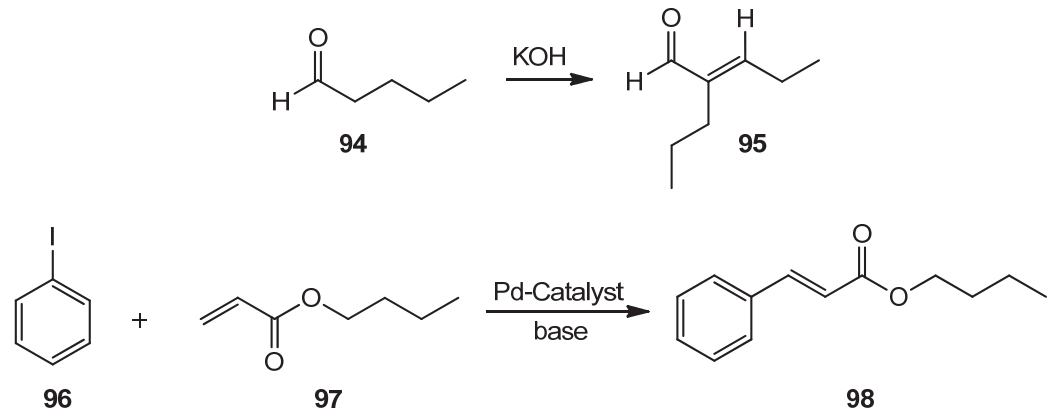
Being non-toxic, biodegradable and non-flammable for which no special handling precautions or storage is required, glycerol has a clear advantage over most organic solvents when it comes to choosing the most environmentally compatible and safe solvent for organic reactions. In particular, the low toxicity of glycerol makes it possible to use it as a solvent in the synthesis of pharmaceutically active ingredients, in which the toxicity and solvent residues have to be carefully controlled. [42] There is also the possibility of recycling glycerol and reusing it in further reactions which is particularly useful in the case of reactions catalysed by transition metal complexes. [2]

Although glycerol exhibits promising features as a sustainable solvent for organic synthesis, the use of glycerol as a solvent also has several well-known drawbacks. Among them are the high viscosity of glycerol and the low solubility of highly hydrophobic compounds and gases, which can cause mass transfer problems and limit its possible applications. If the thermal decomposition of the starting materials or the products isn't a problem, the viscosity issue can be overcome by heating the reaction mixture above 60 °C or by using co-solvents. Also using high-intensity ultrasound (US) or microwave (MW) radiation in a standalone or combined manner to enhance the heat and mass transfer and thus accelerating the reaction rate has been reported to be a successful approach. [2; 43] Another drawback is the chemical reactivity of hydroxyl groups which can lead to the formation of side products or deactivation of some of the reagents used in the reaction. In particular, the three hydroxyl groups of glycerol are reactive in extremely acidic or basic conditions. Because of this, glycerol has to be used as the solvent in chemically inert environment to prevent the hydroxyl groups from reacting. Also the coordinating properties of glycerol can cause problems when transition metal complexes are being used as catalysts. In particular, the deactivation of organometallic complexes can become an issue. [42]

In conclusion, if the issues associated with the high viscosity and reactivity of hydroxyl groups of glycerol can be avoided or overcome, the renewable origin of glycerol and its unique combination of physicochemical properties, make glycerol a good candidate to be employed as a more sustainable reaction medium for synthetic chemistry. [1]

3.3 Performance as a solvent in organic reactions

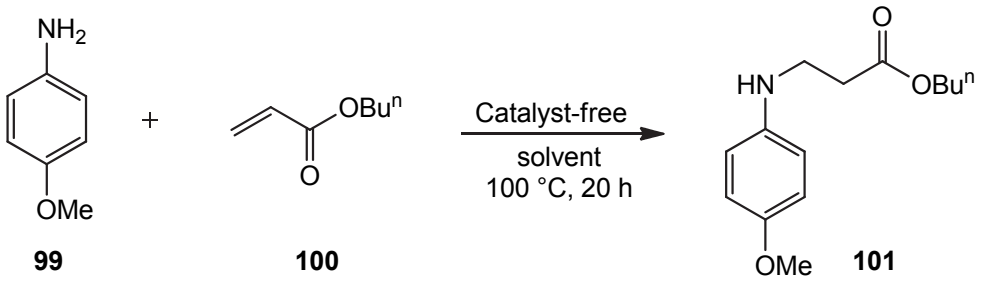
In 2006 Wolfson's group in Israel reported the first example for the use of glycerol as a green reaction solvent. Since then the number of publications dealing with the possible use of glycerol as a sustainable solvent for catalysis and organic chemistry has significantly increased, showing the actual interest of the scientific community for this medium. [50] Wolfson's group showed that some selected organic reactions such as base catalysed aldol condensation, Pd-catalysed Heck CC coupling, Suzuki, and hydrogenation reactions could be performed in glycerol even without any purification. [46; 50]



Scheme 33. *Representative reactions of base catalysed aldol condensation of n-valeraldehyde* ***94*** *and Pd-catalysed Heck coupling of iodobenzene* ***96*** *and butyl acrylate* ***97****.*

The reported results illustrated that pure glycerol gave higher conversions than crude glycerol. They concluded that the residual methanol or water in crude glycerol could not be attributed to the difference in conversion. It was also found that the oil source did not affect the reaction performance. [41] They reported that these catalytic reactions proceeded well in glycerol and high yields could be obtained showing that glycerol could be used as a replacement for traditional organic solvents. In these reactions glycerol was found to be stable and the isolation of reaction products could be achieved by simple liquid-liquid phase extraction with ethers or esters. Although good yields were obtained, no real advantage in terms of reaction selectivity or catalyst activity was highlighted. Nevertheless this study demonstrated for the first time the feasibility of using glycerol as a solvent, awakening the interest of other researchers for this possible green alternative for traditional organic solvents.

In 2008, Gu and Jérôme reported that glycerol may offer remarkable advantages over conventional or known solvent systems. In particular, they reported that an aza-Michael reaction between p-anisidine **99** and n-butyl acrylate **100** can successfully proceed under catalyst-free conditions using glycerol as the only solvent. [46]

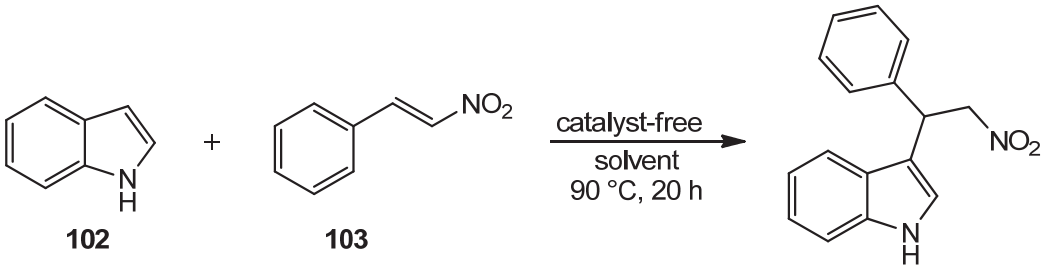


In glycerol: Yield = 82 %;
In crude glycerol Yield = 81 %;
In 1,2-propanediol: Yield = 30 %;
In water or under solvent-free considtions: Yield < 5 %;
In toluene, DMSO, DMF or DCE (90 °C): no product.

Scheme 34. *Aza-Michael reaction of p-anisidine* ***99*** *in different solvent systems. [46]*

Remarkably, while high yield (>80 %) was obtained either in pure glycerol or in technical grade glycerol under standard conditions (100 °C and 20 h), only a trace amount of product was obtained in water or under solvent-free conditions. Many organic solvents such as toluene, DMF, DMSO and 1,2-dichloroethane were all ineffective for this reaction.

A similar trend was observed in the Michael addition of indole **102** to nitrostyrene **103**, in which only glycerol was found to be capable of affording the desired product **104** in ca. 80 % yield under catalyst-free conditions (Scheme 35). [42]



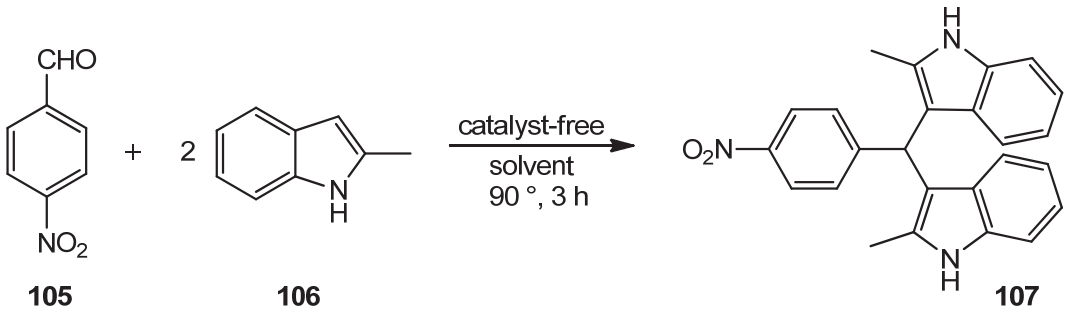
In glycerol: Yield = 80 %;
In crude glycerol: Yield = 78 %;
In toluene, DMF or under solvent-free conditions: Yield < 5 %;
In water: Yield = 55 %.

Scheme 35. *Michael reaction of indole* ***102*** *in different solvent systems. [42]*

Also the product isolation and recycling of glycerol were conveniently achieved by means of liquid-liquid phase extractions with ethyl acetate.

In the electrophilic activations of aromatic aldehydes with indoles or 1,3-cyclohexanediones, glycerol has also been proven to be an advantageous solvent. Generally these reactions are carried out in the presence of acid catalysts, however the desired product was obtained in 95 % yield when using glycerol as the solvent, and 4-

nitrobenzaldehyde **105** and 2-methylindole **106** as reactants under optimised conditions (90 °C and 3 h) without the assistance of any catalyst. (Scheme 36).



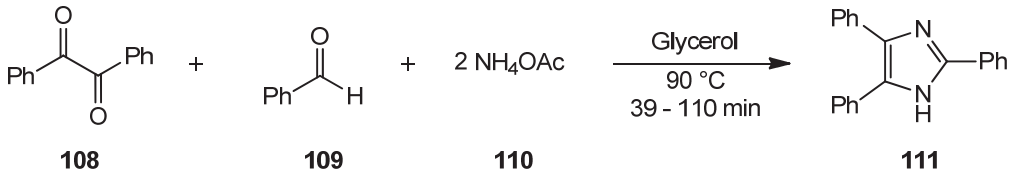
105 **106** **107**

Toluene, DMF, DMSO, n-butyl acetate, no solvent: Yield < 5 %;
n-butanol: Yield = 38 %;
H_2O: Yield = 76 %;
Polyethylene glycol and ethylene glycol: Yield = 85 %;
Glycerol: Yield = 95 %.

Scheme 36. *Reaction between 4-nitrobenzaldehyde **105** and 2-methylindole **106** in different solvent systems under catalyst-free conditions. [42]*

Other solvent systems such as toluene, DMF, DMSO, n-butyl acetate, *n*-butanol and water were also examined but in all cases the targeted product was obtained either in a trace amount or in a significantly lower yield than in glycerol. The products formed were insoluble in glycerol so the isolation of reaction products was conveniently achieved by filtration after dilution in water. The advantages of glycerol for this reaction include the absence of acid catalysts which not only simplifies the work-up procedure and minimizes the generation of waste but also allows the use of acid-sensitive substrates. Also the reaction products were easily separated and no volatile organic solvent were needed for the isolation process. However this method also has shortcomings: for products that cannot precipitate in glycerol, organic solvents have to be used in order to extract them. Also the use of glycerol as the solvent doesn't work for some less-reactive substrates and in these cases addition of a Lewis acid such as $CeCl_3 \cdot 7H_2O$, was necessary to improve the reaction yield. [42]

A simple, efficient and catalyst-free method was developed by Nemati *et al*. for the synthesis of 2,4,5-triaryl and 1,2,4,5-tetraaryl imidazole derivatives in glycerol as the green solvent at 90 °C. In order to test the feasibility of this method they prepared 2,4,5-triphenyl-1H-imidazole **111** according to scheme 37.



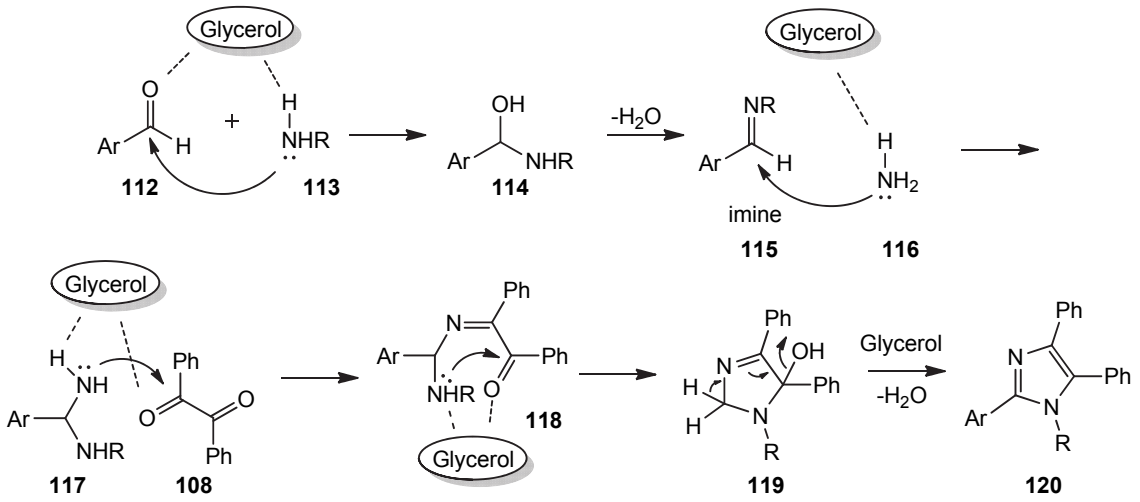
Scheme 37. *Synthesis of 2,4,5-triphenyl-1H-imidazole* ***111****. [42]*

In this reaction the yields of products were comparable to or better than those in conventional solvents. [44] The role of glycerol in this multi component reaction was established by the fact that in the absence of glycerol, the reaction proceeded sluggishly (Table 4, entry 10).

Table 4. *Reaction conditions evaluation for imidazole synthesis represented in Scheme 37. [44]*

Entry	Solvent	Condition (°C)	Time	Yield of 111 (%)
1	MeOH	63	5 h	25
2	EtOH	75	5 h	47
3	Acetonitrile	78	5 h	40
4	DMF	110	5 h	43
5	PEG-400	120	1.5 h	88
6	Glycerol	RT	1.5 h	52
7	Glycerol	70	1.5 h	69
8	Glycerol	90	43 min	94
9	Glycerol	110	43 min	83
10	Solvent-free	90	43 min	Trace

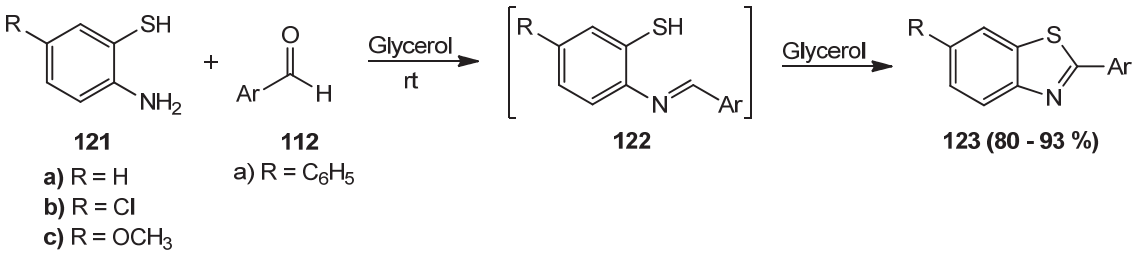
It can be seen that glycerol is indeed an essential component of the reaction. As shown in Table 4 (entries 1 and 2), the reaction did proceed in reflux EtOH or MeOH as protic solvents, but with low yields even after 5 h. It was suspected that the poor yields in hydroxylic and polar solvents were probably due to the lower solubility of the starting materials in these solvents, coupled with the fact that ammonium acetate is solvated in hydroxylic solvents, thereby reducing its effective reactivity with ammonia. [44] They suggested that the hydrogen of the hydroxyl group of glycerol through the formation of powerful hydrogen bonding activates the carbonyl compounds. At the same time the oxygen of the hydroxyl group of glycerol forms a hydrogen bond with the hydrogen of the amine weakening the N–H bond enhancing the nucleophilicity of nitrogen for addition to the carbonyl group of the aldehyde (Scheme 38).



Scheme 38. *The proposed mechanism for scheme 37. [44]*

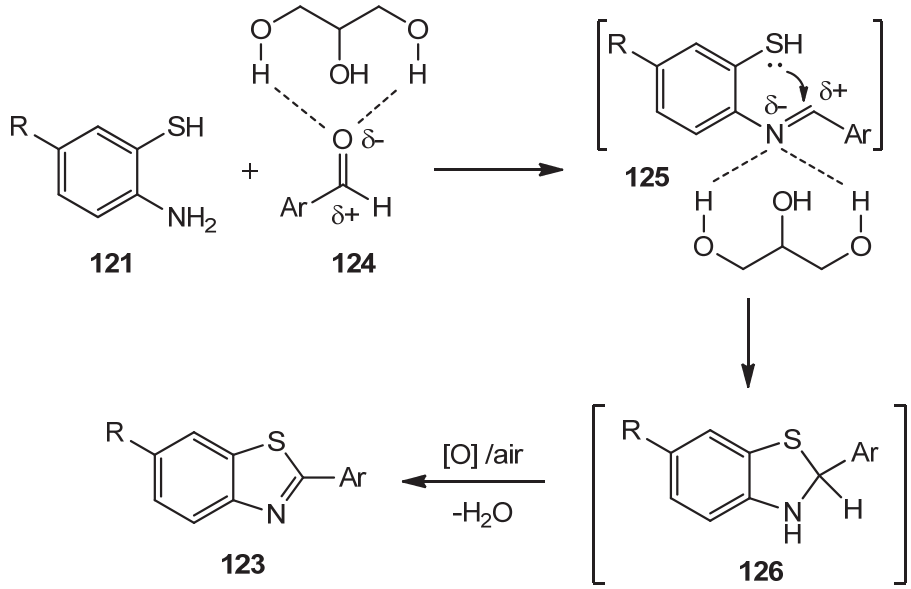
It was also proposed that increasing the reaction temperature decreased the yield of the products because the hydrogen bonds were weakened (Table 4, entry 9). [44]

Sadek *et al.* reported on a one-pot, catalyst-free and clean synthesis of 2-arylbenzothiazoles **123** via the ambient temperature reaction of 2-aminothiophenols **121** and aromatic aldehydes **112**. [41]



Scheme 39. *One-pot synthesis of 2-arylbenzothiazoles **123**. [41]*

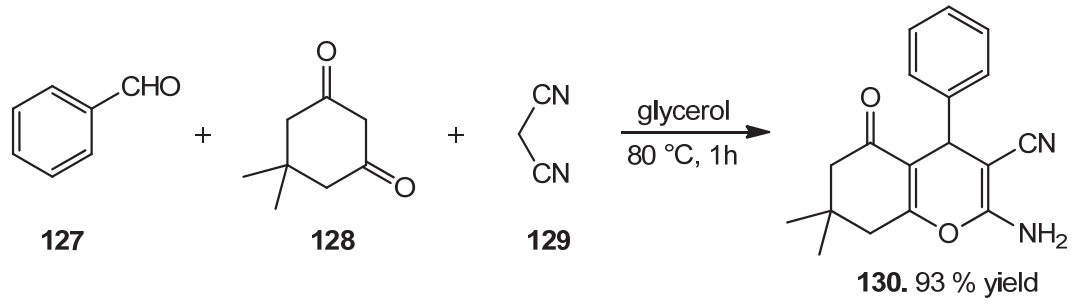
When a mixture of **121**a and **112a** in glycerol was stirred at room temperature, it was observed that reactants were recovered almost unchanged after a long period of time. The reaction promoted by just heating the reaction mixture until the reactants were dissolved and then left at room temperature for 30 min afforded the product in excellent yield. When the same reaction was carried out in different solvents, such as H_2O, acetone and $CHCl_3$ under the same reaction conditions, the reactants were recovered almost unchanged. A mechanism to account for the formation of 4 is postulated in Scheme 40. [41]



Scheme 40. *A proposed mechanism for the formation of 2-arylbenzothiazoles* ***123****. [41]*

The reactants readily dissolve into glycerol making them easily available to interact with the solvent. According to the authors, the carbonyl carbon of the aldehyde will be activated because of the intermolecular hydrogen bonding with the hydroxyl groups of glycerol. In addition, the formed intermediates could be stabilized by several types of complexations and hydrogen bonding with the hydroxyl groups of glycerol. [41]

One of the widest applications of glycerol as a solvent in non-catalysed organic synthesis is the preparation of heterocyclic compounds by condensation procedures. [2] For instance, Safaei *et al*. reported a highly efficient method for the one-pot three-component synthesis of 4*H*-pyran derivatives using glycerol as a reaction solvent. (Scheme 42).

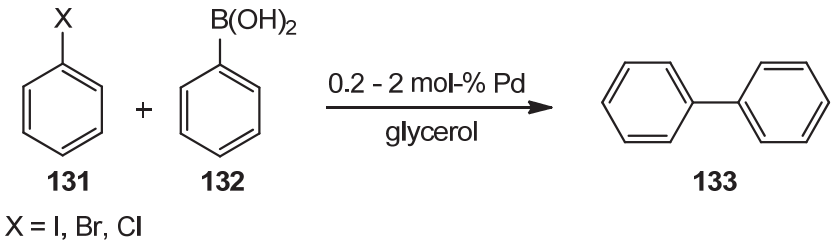


Scheme 42. *Non-catalysed one-pot three-component synthesis of 4H-pyran derivatives in glycerol. [2]*

Glycerol gave much better results at lower temperature and reaction time than traditionally used organic solvents such as ethanol, toluene or DMF, outperforming ethylene glycol and water. [2] The examples mentioned above demonstrate that glycerol can be used as a promoting medium for organic reactions even without the use of catalyst sim-

plifying the work-up procedure and consequently increasing the greenness of the synthetic reactions.

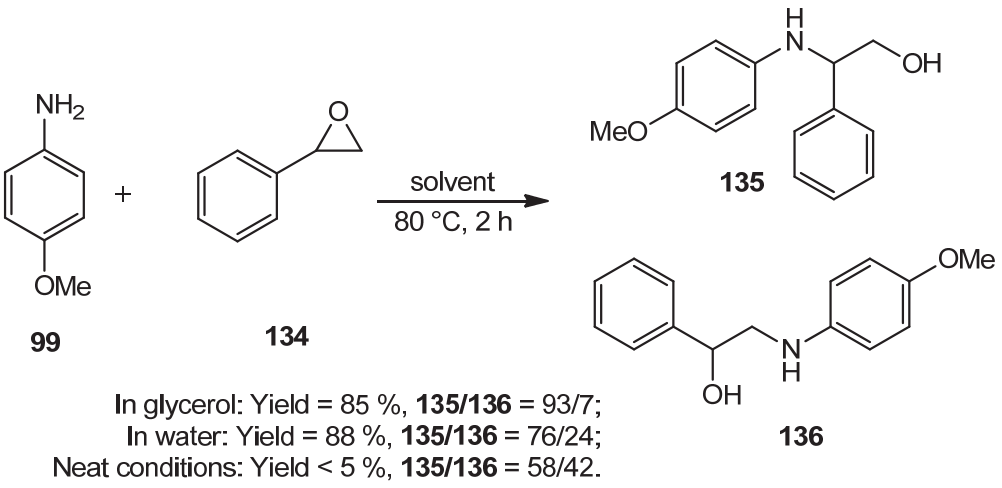
Heterogeneous catalysts can also be used in combination with glycerol which was explored in a recent study, where several examples of organic transformations carried out in glycerol with the help of heterogeneous catalysis combined with ultrasound (US) and microwaves (MW) activation were given. [55] One of these transformations is the palladium-catalysed Suzuki cross-coupling reaction which is shown in Scheme 43.



Scheme 43. *Palladium-catalysed Suzuki cross-coupling reaction in glycerol. [52]*

The enhanced reaction rates were obtained in order US + MW > US > MW, with regard to the thermally activated reactions. [2]

When a reaction is performed in a liquid phase, the solvent can dramatically impact the reaction selectivity in addition to the reaction rate. [42] In this context, promising results for glycerol as a solvent have been obtained for example in the ring-opening of *p*-anisidine **99** with styrene oxide **134**. The reaction is generally catalysed by Lewis or Brønsted acids but it can also be performed in the absence of catalyst either in glycerol or in water.



Scheme 44. *Ring-opening of styrene oxide **134** by p-anisidine **99**. [42]*

Interestingly, under identical conditions, the regioselectivity obtained in glycerol is higher than that in water (Scheme 44). [42] Even though there is no explanation yet for this observed result, it shows that glycerol can indeed also affect the reaction selectivity.

Recently, Wolfson *et al.* investigated the Baker's yeast catalysed asymmetric reduction of methyl acetoacetate in aqueous glycerol. They reported that the concentration of glycerol in the solution affected the extraction yields. Mixtures containing 25 - 75 % glycerol in water were found to be the most beneficial. A similar effect was observed for the extraction of 2-butanol from a water/glycerol solution with diethyl ether. The extraction yields of 2-butanol from water or glycerol alone were 20 % and 26 % respectively whereas extraction from 50 wt% water/glycerol solution resulted in significant 50 % increase in yield. [42]

Although glycerol has been proven to be capable of promoting many organic reactions, no definitive information is available at the moment for the reasons behind these promising results. In the literature a similar trend has been observed using water as a solvent and many efforts have been made to better understand the mechanism of water in organic reactions. These studies with water should help to understand the glycerol system since both water and glycerol are characterized by a strong hydrogen bond network. [42]

3.4 Summary

Taking into account the impact of chemical processes on the environment, the search for green solvents has become a great challenge in organic synthesis. Water and biomass-derived chemicals are a promising alternative for these petrochemical-based solvents and they exhibit many advantages such as biodegradability, low vapour pressure and high boiling point.

Glycerol has recently emerged as an economically appealing and safe solvent for organic synthesis. Several catalytic and non-catalytic reactions have been successfully performed in glycerol with high product yields and selectivities and in some cases, glycerol has even been found to enhance the effectiveness and selectivity of the reactions.

From a social and economic point of view, utilization of glycerol takes place as one of the most urgent topics in the beginning of this century. The rapid development of the vegetable oil industries as well as the emergence of other large-scale processes based on the conversion of cellulose and lignocelluloses generates a tremendous amount of crude glycerol as a by-product which is now in urgent need of chemical utilisation. Additionally, the development of the third generation feedstock for biodiesel production using microalgae or land plants unsuitable for food are expected to increase the commercial quantities of biodiesel in the upcoming years.

The direct utilization of glycerol as a green solvent for organic transformations would offer a sustainable medium for some organic transformations with more hydrophobic substrates than those commonly used in water. [46] Even if this topic does not aim to consume glycerol as a reactant, the direct use of glycerol as a solvent offers an undeniable economically and environmentally viable application.

Despite the promising features of glycerol, much effort has to be made in the future to extend its use as a green solvent. Until now reasons behind the promoting effect of glycerol are still undiscovered and finding out the reasons behind this “magic solvent effect” as in the case of water might take years. It is possible that the strong hydrogen bond network of glycerol might be responsible for this rate enhancement. However this might also be explained by the presence of impurities in glycerol.

Within the framework of green chemistry, the possible and direct utilization of technical grade glycerol as a green solvent is even more desirable but successful examples are so far scarce. Even if pharmaceutical grade glycerol is very cheap, purification of technical grade glycerol, being an energy-consuming process, isn’t usually an economically viable alternative and it affects the whole environmental impact of all glycerol-based processes. Therefore, many efforts have to be directed towards the possible use of technical grade glycerol as a solvent.

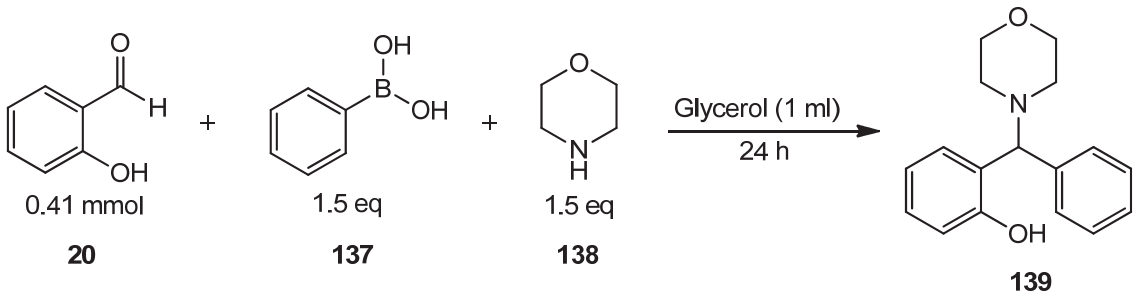
Despite these challenges, using glycerol as a solvent clearly offers new opportunities in the search of innovative solutions for the replacement of volatile organic solvents by greener alternatives. More generally, using glycerol as a solvent adds to the library of the available green solvents for organic synthesis and at the moment, glycerol seems to be the only green solvent like water that can combine low price with low toxicity. [42] In this context, glycerol has all the features to become a central green solvent not only in catalysis or organic chemistry but also in materials chemistry and in biology alike.

4. RESULTS AND DISCUSSION

The experimental part of this thesis was done in the synthesis laboratory of the Department of Chemistry and Bioengineering in Tampere University of Technology during January - April 2014. This section contains the results and discussion of the syntheses done. The detailed description of the syntheses of individual compounds has been collected to the experimental section of this thesis.

4.1 The optimisation of reaction conditions

Before the experimental work for this thesis was started, the reaction conditions for the Petasis-Borono Mannich reaction in glycerol were already optimised. The screening of reaction conditions was done for the reaction shown in scheme 45.



Scheme 45. *The reaction used for the screening of optimal reaction conditions.*

First the most optimal reaction temperature was investigated according to table 5.

Table 5. *the screening of optimal reaction temperature*

Entry	Temperature	Isolated Yield (%)
1	rt	38
2	50	56
3	80	42
4	100	44
5	120	44

As can be seen the reaction temperature of 50 °C (entry 2) gave the highest yield while raising the reaction temperature lowered the yield slightly (entries 3-4). Next the optimal ratio of starting materials was investigated in 50 °C and the results are shown in table 6

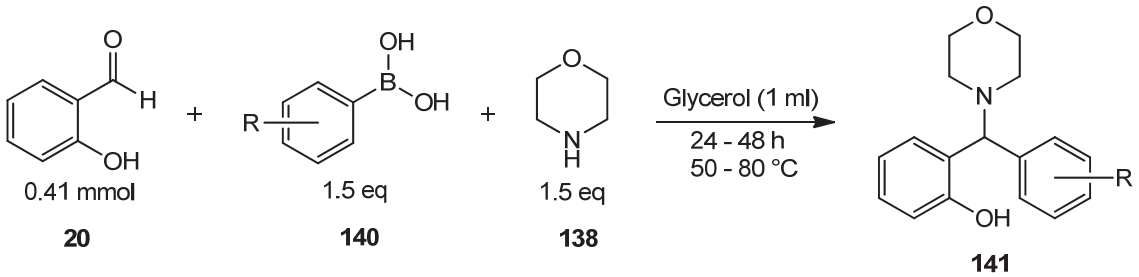
Table 6. *The screening for optimal ratio of starting materials.*

Entry	Boronic acid (eq)	Amine (eq)	Aldehyde (eq)	Isolated Yield (%)
1	1.2	1.2	1	56
2	1.5	1.5	1	66
3	1.5	1	1.5	53
4	1	1.5	1.5	70
5	1.5	1	1	46
6	1	1.5	1	56
7	1	1	1.5	43

Even though entry 4 where the boronic acid is the limiting reagent and 1.5 eq of amine and aldehyde is used gave the highest yield, it was decided to use the salicylaldehyde as the limiting reagent because its amount in the reaction mixture was easier to monitor by TLC. Entry 2 gave the product in almost as high yield as entry 4 so that ratio of starting materials was chosen for the remaining of this thesis.

4.2 The effect of the arylboronic acid

In order to see how different substituents in the arylboronic acid **140** would affect the outcome of the Petasis-Borono Mannich reaction in glycerol, several arylboronic acids were mixed with salicylaldehyde **20** and morpholine **138** according to the reaction scheme 46.



Scheme 46. *The reaction scheme for the experiments with different arylboronic acids.*

Plain phenylboronic acid **137** was used as a reference compound (Table 7, entry 1) giving the product, 2-(morpholino(phenyl)methyl)phenol **139** in 75 % yield after 48 hours in 50 °C. This yield is comparable to the reported yields obtained in different solvents even though the reaction time was longer in glycerol. [11; 20; 30] The results obtained with differently substituted aryl boronic acids have been collected to Table 7.

Table 7. *The yields obtained with different arylboronic acids.*

Entry	R	Reaction Conditions	Yield (%)	Compound
1	H	48 h, 50 °C	75	**139**
2a	4-Cl	48 h, 50 °C	59	**141a**
2b		48 h, 80 °C	72	
3a	4-NO_2	48 h, 50 °C	14	**141b**
3b		48 h, 80 °C	34	
3c		72 h, 80 °C	25	
4	4-MeO	48 h, 50 °C	77	**141c**
5	4-Me	24 h, 50 °C	86	**141d**
6	2,6-Me	48 h, 50 °C	11	**141e**
7	2,4,6-Me	48 h, 50 °C	17[1]	**141f**
8	4-Ac	48 h, 50 °C	27	**141g**
9	4-vinyl	48 h, 50 °C	76	**141h**

1: Some product lost due to poor separation of the product and the aldehyde during flash chromatography

Many conclusions can be drawn from the table 7 above. As has been reported in literature [20; 30], electron withdrawing groups (EWG) in the phenyl ring of the boronic acid lowered the yields drastically in the same reaction conditions (entries 2a and 3a). As can be expected, the effect isn't as strong with chlorine, since it is *para*-directing despite its electron withdrawing nature and not being as deactivating as the nitro group. Raising the reaction temperature to 80 °C managed to cancel this deactivating effect with 4-chlorophenylboronic acid, performing almost as well as the phenylboronic acid in the lower temperature (entry 2b). Raising the reaction temperature improved the yield also with 4-nitrophenylboronic acid (entry 3b) although the overall yield was still poor. Trying to improve the yield further by raising the reaction time from 48 hours to 72 hours in 80 °C only lowered the yield probably due to product decomposition (entry 3c).

4-Acetyl group was also found unsurprisingly to give low yield because of its EWG and *meta*-directing nature. It is also possible that the carbonyl moiety in the acetyl group could take part in unwanted side reaction even though no sign of this was seen on the TLC plates during the reaction.

Aryl activating groups in the boronic acid were not found in every case to promote the reaction as well as expected. 4-Tolylboronic acid (entry 5) increased the yield as was expected from an electron donating (EDG) methyl group in the *p*-position giving the product in 86 % yield after only 24 hours. However, for reasons unknown, 4-methoxy (entry 4) and 4-vinyl (entry 9) groups did not increase the yield noticeably from the yield given by phenylboronic acid even after 48 hours.

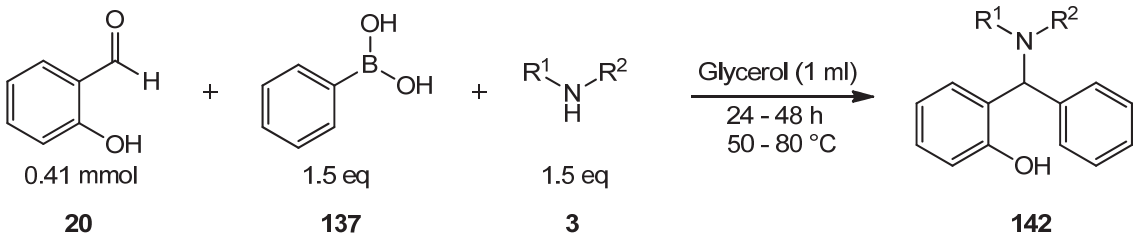
Di- and tri-methyl-substituted 2,6-dimethyl arylboronic acid (entry 6) and 2,4,6-trimethyl arylboronic acid (entry 7) gave the desired products in very low yields. Even though some product was lost in the case of 2,4,6-trimethyl arylboronic acid due to poor

separation of the aldehyde and the product during purification by flash chromatography, the major cause for the drop in yields is most likely due to steric effects caused by the two methyl groups in the *ortho*-positions making the migration of the phenyl group of the boronic acid to the iminium species energetically unfavourable.

In most cases shown in table 7 the reaction had not gone to completion in 48 hours when the reactions were at the latest quenched. It was observed in several cases that the aldehyde component was completely consumed, as judged by TLC, although the yields remained lower than 90 %. This would hint that either the products are being lost during the work-up or purification process or that the salicylaldehyde, which is the limiting reagent used to monitor the reaction completion, or the iminium intermediate is reacting with something else in the reaction mixture, for example with glycerol.

4.3 The effect of the amine

The effect of different amines on the PBM reaction in glycerol was investigated according to the reaction scheme 47 below. Only cyclic and acyclic secondary amines were investigated based on the many reports on the ineffectiveness of primary amines in the PBM reaction. [11; 22; 29] The results acquired are presented in the table 8.



Scheme 47. *The reaction scheme for the experiments with different amine components.*

Table 8. *The yields obtained with different amines.*

Entry	Amine	Reaction Conditions	Yield (%)	Compound
1	morpholine	48 h, 50 °C	75	**139**
2	piperidine	48 h, 50 °C	49	**142a**
3a	pyrrolidine	48 h, 50 °C	59	**142b**
3b		24 h, 80 °C	44	
4a	dibenzylamine	48 h, 50 °C	54[1]	**142c**
4b		48 h, 50 °C	62[2]	
4c		48 h, 50 °C	63[3]	
5	diallylamine	48 h, 50 °C	51	**142d**
		48 h, 50 °C	44	
6	*N*-benzylmethylamine	48 h, 50 °C	76	**142e**
		24 h, 80 °C	60	
7	indoline	48 h, 50 °C	94	**142f**

1: Product lost due to dragging in the column during purification.

2: Product dragging prevented with the use of more polar eluent during flash chromatography.

3: 1.5 eq of dibenzylamine added in the beginning of the reaction and followed by 1.0 eq after 24 hours.

Unexpected results were obtained while different amines were investigated and drawing conclusions from them turned out to be challenging. Piperidine (entry 2) was expected to work better compared to morpholine (entry 1) because of its more nucleophilic nature which would promote its attack to the carbonyl carbon of the salicylaldehyde. However an opposite trend was observed, morpholine giving the product in 75 % yield while piperidine ended up giving the product only in 49 % yield. Likewise pyrrolidine (entry 3a) gave the product only in 59 % yield and raising the reaction temperature to 80 % (entry 3b) lowered the yield even though according to TLC all of the aldehyde was consumed only after 24 hours.

Dibenzylamine (entry 4a-c) and diallylamine (entry 5) were also found to be less effective than morpholine which would be expected considering that cyclic amines are more nucleophilic with their alkyl substituents tied back, leaving the free electron pair of the nitrogen more exposed. To test whether glycerol could be binding with the amine and preventing it from reacting with the aldehyde, first 1.5 eq of dibenzylamine was added to the reaction vessel, followed by the addition of extra 1.0 eq after 24 hours. However, no difference in yield was observed (entry 4c). *N*-benzylmethyl amine (entry 6) was found to be more successful giving the product in 76 % yield. However, once more the attempt trying to increase the reaction temperature ended up lowering the yield while the reaction seemed to have been completed according to TLC.

Indoline (entry 7) was the only amine used that clearly outperformed morpholine in reaction performance giving the end product in 94 % yield after the reaction seemed to

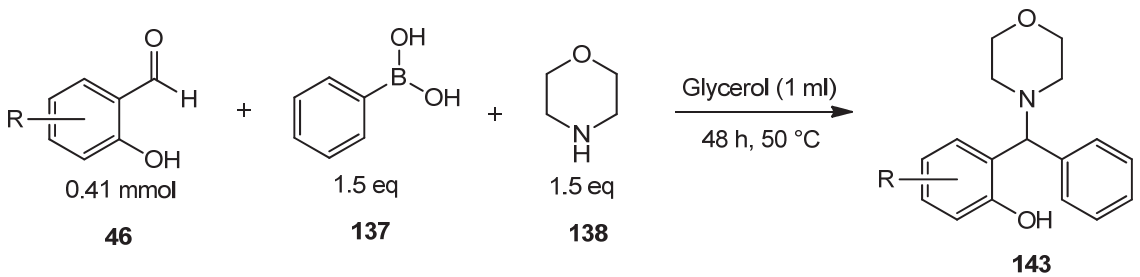
have been completed according to TLC after 48 hours. The reason for this notable increase in yield is unknown and more experiments should be done with substituted indolines and alkyl anilines to find out the extent of this promoting effect.

The formation of by-products was observed on TLC plates with most of the amines, while this was not generally observed when experimenting with morpholine (entry 1) and different boronic acids (table 7). It would seem that the amines or the iminium intermediates formed are taking part in side reactions possibly with glycerol lowering the yield of the desired Petasis product. Isolation and structural analysis of these by-products could possibly help to elucidate the solvent effects that glycerol has for the PBM reaction.

Even though many of the entries shown in the table 8 above were reported to work better than morpholine (entry 1) in water [20], the PBM reaction has been shown to be highly dependent on the solvent and reaction conditions used. [10; 20 - 22] For example similar trend to the results shown in table 8 were reported in solvent free conditions [30] with morpholine outperforming pyrrolidine, piperidine, dibenzylamine and *N*-benzylmethylamine alike.

4.4 The effect of the salicylaldehyde

In order to also get a small look on what effects the substituents in salicylaldehyde **46** have on the reaction outcome, 2-hydroxy-4-methoxybenzaldehyde and 2-hydroxy-5-nitrobenzaldehyde were tested according to the reaction scheme 48. These were the only substituted salicylaldehydes used, since they were readily available in the lab and preparing other aldehydes wouldn't have been possible in the time frame of the thesis. In order to get a better idea of the effects that the substituents in the salicylaldehyde have on the reaction, more aldehydes would have to be tested in the future.
The results are shown in table 9 along with the unsubstituted salicylaldehyde (table 9, entry 1) which was used as a reference compound.



Scheme 48. *The reaction scheme for the experiments with different salicylaldehydes* ***46****.*

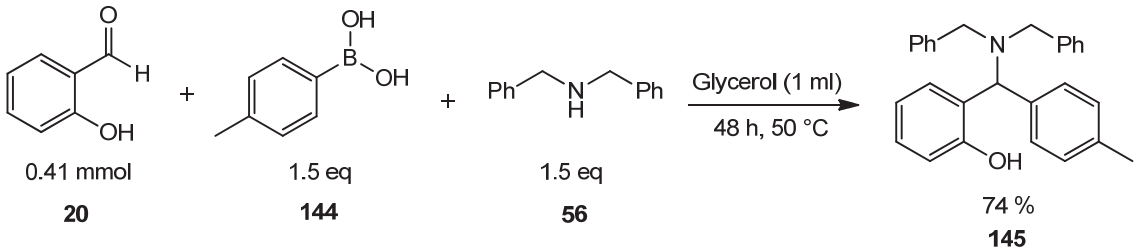
Table 9. *The yields obtained with differently substituted salicylaldehydes.*

Entry	R	Reaction Conditions	Yield (%)	Compound
1	H	48 h, 50 °C	75	**139**
2	4-MeO	48 h, 50 °C	58	**143a**
3	5-NO_2	48 h, 50 °C	66	**143b**

From the two examples presented in table 9, it can be seen that both substituted salicylaldehydes decreased the yield (entries 2, 3). The same effect has been reported in the literature for 4-Me and 3,5-di-*tert*-butyl groups. [30] The decrease in yield with 4-MeO group can be at least in part explained by the decreased electrophilicity of the carbonyl carbon of the salicylaldehyde due to the electron donating nature of the methoxy group in the *p*-position. This would affect the nucleophilic attack of the amine species to the carbonyl carbon of the salicylaldehyde and hinder the migration of the phenyl substituent of the boronic acid to the iminium intermediate. Following the same train of thought, the nitro group could make the carbonyl carbon more electrophilic promoting the attack of the amine to it but at the same time pulling the electron density away from the oxygen of the hydroxyl group hindering the coordination of the iminium species to the boronic acid.

4.5 Mixed reactions

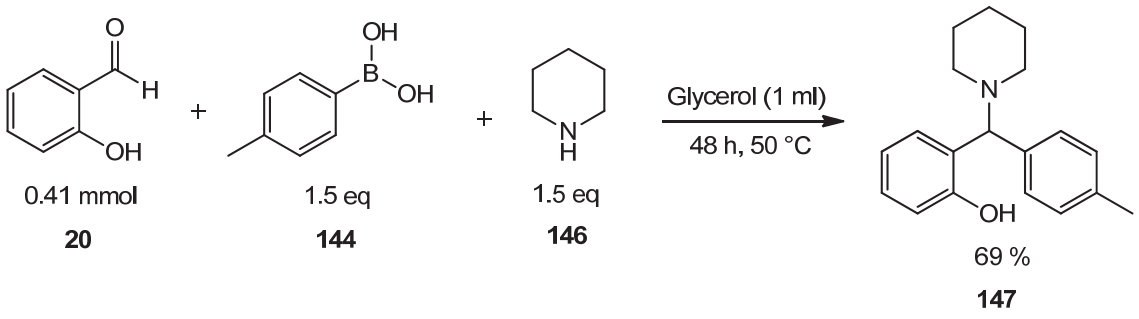
After the initial screening of the effects that the separate substituents would have on the reaction yield, a handful of starting materials were mixed in order to increase the diversity of the product library already acquired. First because of the surprisingly low yield obtained with dibenzylamine earlier (table 8, entry 4a-d), salicylaldehyde **20** was mixed with dibenzylamine **56** and *p*-tolylboronic acid **144** according to scheme 49 to see if the ring-activating nature of 4-methyl group in the boronic acid would increase the yield.



Scheme 49. *The synthesis of 2-((dibenzylamino)(p-tolyl)methyl)phenol **145**.*

The yield improved noticeably with the addition of the 4-methyl group to the boronic acid as expected, giving the product in 74 % yield though still much lower than the 99 % yield reported when water was used as the reaction medium. [20]

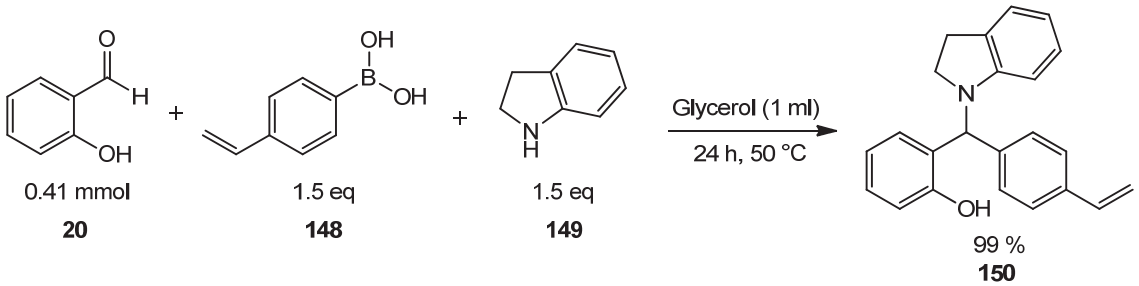
Because of the low yield obtained also with piperidine **146** (table 8, entry 2), the same approach was taken to try to increase the yield with the said amine according to scheme 50.



Scheme 50. *The synthesis of 2-(piperidin-1-yl(p-tolyl)methyl)phenol **147**.*

The yield was again higher with the addition of the 4-methyl group to the boronic acid but a lot lower compared to the reaction yield of 96 % when performed in water. [20]

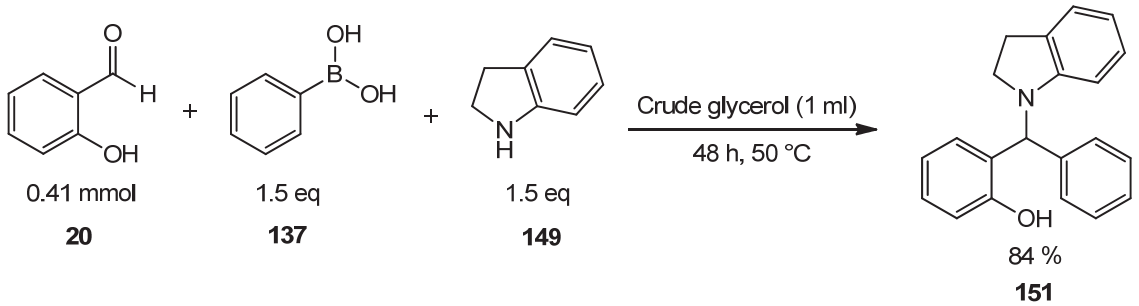
Encouraged by the excellent yield obtained with indoline **149** (table 8, entry 7) and 4-vinylboronic acid **148**, these two were mixed with salicylaldehyde **20** according to the scheme 51.



Scheme 51. *The synthesis of 2-(indolin-1-yl(4-vinylphenyl)methyl)phenol **150**.*

As can be seen the product 2-(indolin-1-yl(4-vinylphenyl)methyl)phenol **150** was obtained in excellent 99 % yield after 24 hours. This result along with the result in table 8, entry 7 and the fact that no examples of the use of indoline was found in literature for this reaction shows that indoline analogues along with alkyl anilines should be investigated further as possibly promising amine components for the Petasis-Borono Mannich reaction at least when glycerol is used as the reaction medium.

Finally as previously mentioned, crude glycerol from biodiesel production contains a various amount of impurities such as methanol, water, catalyst residual and free fatty acids along with their esters and salts which can affect the reaction performance. [43, 50] In order to test if crude glycerol would have any effect on the reaction outcome, salicylaldehyde **20** was mixed with phenylboronic acid **137** and indoline **149** using crude glycerol as the solvent according to the scheme 52 below.

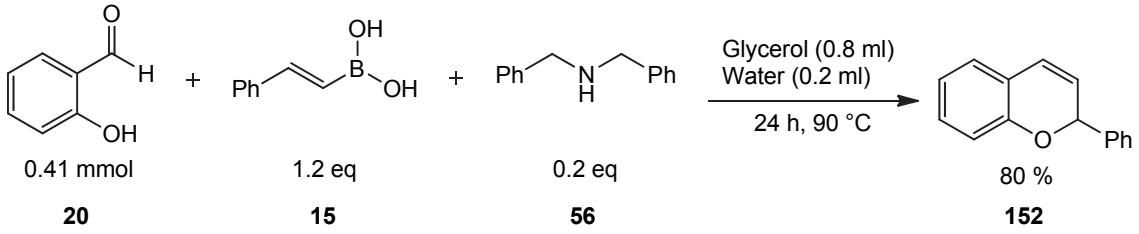


Scheme 52. *The synthesis of 2-(indolin-1-yl(phenyl)methyl)phenol* ***151*** *in crude glycerol.*

The reaction was found to give 2-(indolin-1-yl(phenyl)methyl)phenol **151** in good 84 % yield which was however lower than the 94 % yield got in pure glycerol (table 8. entry 7). Although more experiments would have to be run in order to get a better picture of the effects that the additives in crude glycerol have on the reaction performance, based on the example shown in scheme 52 and as has been reported in the literature for reactions such as aldol condensation Pd-catalysed Heck and Suzuki coupling [50], no promoting effect was observed when crude glycerol was used instead of the pure compound.

4.6 The synthesis of 2-phenyl-2*H*-chromene

As has been reported in the literature, the Petasis-Borono Mannich reaction can be used in the synthesis of 2*H*-chromenes in different solvents [5; 29; 31]. In order to compare the performance of glycerol as the reaction medium for this reaction, 2-phenyl-2*H*-chromene **152** was synthesised according to scheme 53 using glycerol or glycerol/water mixture as solvent giving the product in 80 - 94 % yield. This has been compared in the table 10 to results found in literature for this same reaction.



Scheme 53. *The synthesis of 2-phenyl-2H-chromene* ***152****.*

Table 10. *The yields obtained for the reaction in scheme 53 in different solvents.*

Entry	Solvent	Reaction Conditions	Yield (%)	Ref.
1	glycerol/water 4:1	24 h, 90 °C	80	
2	glycerol	7 h, 90 °C	94	
3	water	24 h, 80 °C	58	[5]
4	dioxane	24 h, 90 °C, resin supported amine	96	[29]

As can be seen from table 10, the yield increased when glycerol/water mixture was used as the solvent for this specific reaction instead of pure water. This shows that glycerol has the potential of being used as a green solvent for the synthesis of *2H*-chromenes, however more experiments would have to be run in order to get a better view on the effect that glycerol has for the reaction as the outcome was reported to depend on the amine used as the catalyst. [*5*]

5. CONCLUSIONS

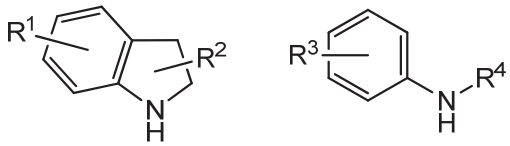
The Petasis-Borono Mannich reaction has been successfully performed using glycerol as solvent. Although the products could be obtained in general in good to excellent yields, the greenness of the process suffers from long reaction times which range from 24 hours to over 48 hours. However, it is possible that the long reaction times could be overcome with microwave activation [11] or with the use of co-solvents.

A range of phenylboronic acids were investigated and it was found, as has been reported in the literature [20; 30], that EDG groups in the aryl ring improved the reaction yield while EWG groups decreased the yield sometimes strikingly. The yields could be improved by raising the reaction temperature.

Steric effects were also found to be of crucial importance since *ortho*-substituents in the phenylboronic acids lowered the yield drastically. These substituents probably hinder the migration of the aryl group from the boronic acid to the iminium species.

Secondary amines were found to be successful in the PBM reaction in glycerol giving yields ranging from 50 % to 94 % when phenylboronic acid was used. However any kind of trend in reactivity was challenging to deduce because no clear difference in reactivity between certain cyclic and acyclic amines was seen even though cyclic amines should have worked better because of their more nucleophilic nature. Piperidine led to the corresponding PBM product in lower yields than other cyclic amines like morpholine and indoline.

Indoline was found to be an excellent amine component for the PBM reaction giving products in over 90 % yield in pure glycerol. Because of this and the lack of examples with this amine in the PBM reaction in the literature, the reactivity of indoline, its analogues **153** and other *N*-alkylanilines **154** should be further investigated.



153 **154**

Scheme 54. *Indoline analogues **153** and N-alkylanilines **154**.*

Substituents in the salicylaldehyde were found to lower the reaction yield. More studies would have to be done in order to get a better general picture of any effect from the aldehyde substituents. The activation of the salicylaldehyde with substituents might turn out to be challenging due to the dual role of the aldehyde in the PBM reaction, first

the carbonyl carbon being the electrophile for the amine and then the *o*-hydroxyl moiety being the nucleophile for the boron species.

It was shown that glycerol promoted the 2*H*-chromene formation better than water, giving the product in good 80 % yield. [5]. Glycerol has the potential of becoming a promising green solvent for 2*H*-chromene synthesis and more experiments should be done to see if even crude glycerol could be used for the synthesis of this biologically important molecule and its derivatives.

The use of crude instead of pure glycerol was found to offer no promoting effects in the PBM reaction and gave the product in slightly lower yield compared to pure glycerol. However in the single experiment done for this thesis, the yield was still high enough (84 %) to warrant more research into using crude glycerol as the reaction medium for the PBM reaction.

It was found interesting that even though in some cases the reaction appeared to have been completed as indicated by the disappearance of the aldehyde spot on the TLC plate, the yields were usually <90 %. This was especially pronounced when different amines were investigated in higher temperatures since the reactions seemed to be completed faster, as was expected, but the yields ended up being worse than in lower temperatures. One reason for this could be that the product is decomposing during the reaction or the workup. In some cases the formation of by-products was observed on TLC plates. This in addition to the aldehyde being used up would hint towards side-reactions happening in the reaction mixture. It is possible that glycerol is reacting with some of the starting materials or with the iminium intermediate, causing the decrease in reaction yield for the desired PBM product.

Even though the formation of by-products lowers the reaction yield, the isolation and structural analysis of these by-products along with Density Functional Theory (DFT) studies about the intermolecular interactions between the reagents and glycerol could possibly help to elucidate the solvent effects that glycerol has in the PBM reaction.

Based on the results and observations made in this thesis, it is safe to say that glycerol can be used as a green solvent for the Petasis-Borono Mannich reaction. Using glycerol in this reaction not only increases the library of possible solvent systems for this useful multicomponent reaction but also further promotes the utilisation of glycerol as a green reaction medium for organic synthesis.

6. EXPERIMENTAL

6.1 General

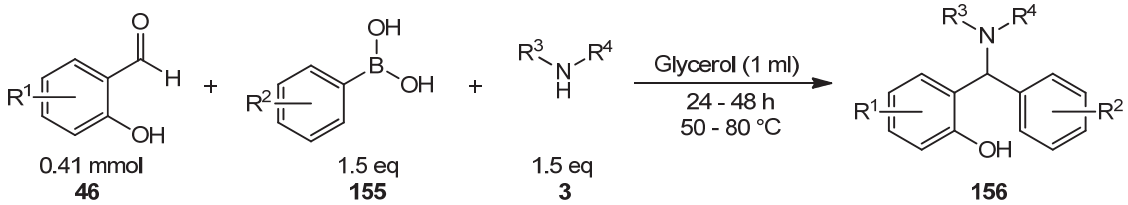
All reactions were performed in air atmosphere in long, capped test tubes. The reagents used were obtained from Sigma-Aldrich except piperidine which was from Fluka. The solvents except for glycerol were also from Sigma-Aldrich. The reagents and solvents were used as obtained unless otherwise stated. Pure glycerol was used as obtained from VWR and the crude glycerol was obtained from Savon Siemen Oy. [53]

Thin-layer chromatography was performed on precoated (Merck TLC silica gel 60 F_{254}) aluminium plates and the detection was done by UV light and the plates were stained with cerium molybdate solution. Flash column chromatography was performed on silica gel 60 (0.040 - 0.063 mm).

^{1}H NMR was measured using Varian Mercury 300 MHz spectrometer and $CDCl_3$ as solvent. The chemical shifts were reported as δ values referenced to internal standard tetramethylsilane. Solvent residues in NMR samples were identified from spectra using article from Gottlieb *et al.* [54].

6.2 Synthesis

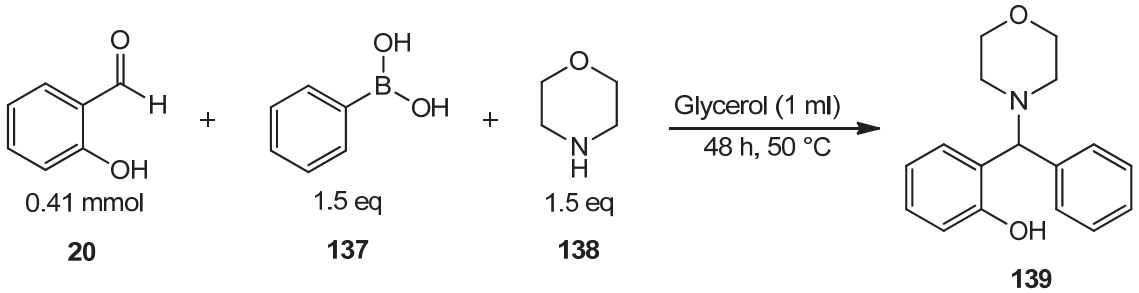
6.2.1 The general procedure



Scheme 55. *The general procedure for the PBM reaction in glycerol.*

The arylboronic acid **155** (1.5 eq) and 1.0 ml of pure glycerol is added into a test tube with a magnetic stirrer and placed in the heated oil bath. The boronic acid is left to dissolve for about 5 minutes after which the aldehyde **46** (0.41 mmol, 1.0 eq) is added to the reaction mixture and the mixture is left to mix for a couple of minutes. Finally, the amine **3** (1.5 eq) is added and the mixture is left to react in the oil bath while the progress of the reaction is being monitored by TLC. After 48 hours or earlier if the reaction has been completed, the reaction is quenched with 1.0 ml of water and 1.0 ml of saturated $NaHCO_3$ solution. The crude product is extracted with 3-5 x 5 ml of diethylether until no product can be detected in the extracted organic phase with TLC. The excess solvent is evaporated using rotavapor and the crude product is dried under vacuum. The product is purified with flash column chromatography using Hex/EtOAc solution as eluent.

6.2.2 2-(Morpholino(phenyl)methyl)phenol (139)



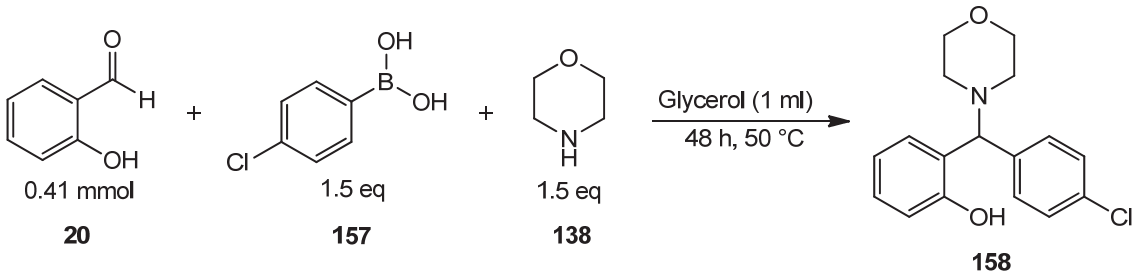
Scheme 56 *The synthesis of 2-(Morpholino(phenyl)methyl)phenol* ***139***

Phenylboronic acid **137** (0.075 g, 0.615 mmol, 1.5 eq) and 1.0 ml of pure glycerol was added into a test tube with a magnetic stirrer and placed in 50 °C oil bath for 5 minutes until some of the boronic acid had dissolved. Next salicylaldehyde **20** (0.044 ml, 0.41 mmol, 1.0 eq) was added to the reaction mixture and the mixture was left to mix for a couple of minutes. Finally, morpholine **138** (0.054 ml, 0.615 mmol, 1.5 eq) was added to the mixture and left to react in the oil bath while the progress of the reaction was monitored by TLC. After 48 hours, even though the reaction hadn't finished, the reaction was quenched with 1.0 ml of water and 1.0 ml of saturated $NaHCO_3$ solution. The

crude product was extracted with 3-5 x 5ml diethylether until no product could be detected in the extracted organic phase with TLC. The excess solvent was evaporated using rotavapor and the crude product dried in vacuum. The product was purified by flash column chromatography using Hex : EtOAc 8 : 2 as eluent obtaining the product in 75 % yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 11.73 (s, 1H), 7.49 - 7.37 (m, 2H), 7.37 - 7.21 (m, 3H), 7.19 - 7.04 (m, 1H), 6.98 - 6.80 (m, 2H), 6.73 (dt, *J*=1.2, 7.5 Hz, 1H), 4.41 (s, 1H), 3.83 - 3.65 (m, 4H), 3.02 - 2.16 (m, 4H) ppm. Appendix 1. NMR in accordance with Wang *et al.* [29]

6.2.3 2-((4-Chlorophenyl)(morpholino)methyl)phenol (158)

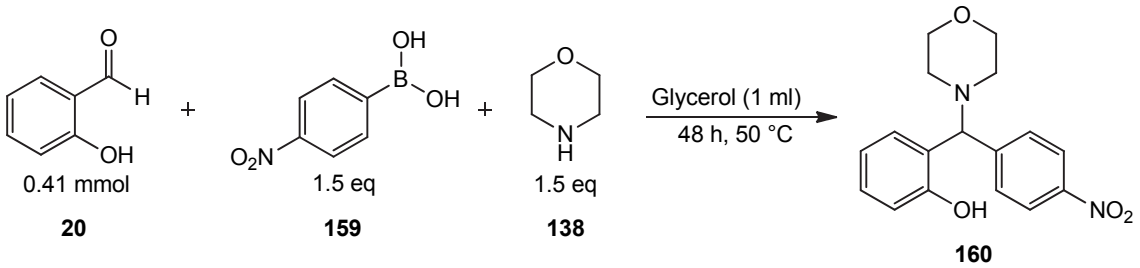


Scheme 57. *The synthesis of 2-((4-Chlorophenyl)(morpholino)methyl)phenol* ***158***

4-Chlorophenylboronic acid **157** (0.096 g, 0.615 mmol, 1.5 eq) and 1.0 ml of pure glycerol was added into a test tube with a magnetic stirrer and placed in 50 °C oil bath for 5 minutes until some of the boronic acid had dissolved. Next salicylaldehyde **20** (0.044 ml, 0.41 mmol, 1.0 eq) was added to the reaction mixture and the mixture was left to mix for a couple of minutes. Finally, morpholine **138** (0.054 ml, 0.615 mmol, 1.5 eq) was added to the mixture and left to react in the oil bath while the progress of the reaction was monitored by TLC. After 48 hours even though the reaction hadn't finished, the reaction was quenched with 1.0 ml of water and 1.0 ml of saturated $NaHCO_3$ solution. The crude product was extracted with 3-5 x 5ml diethylether until no product could be detected in the extracted organic phase with TLC. The excess solvent was evaporated using rotavapor and the crude product dried in vacuum. The product was purified by flash column chromatography using Hex : EtOAc 8 : 2 as eluent obtaining the product in 59 % yield. The same procedure was repeated in 80 °C for 48 hours yielding the product in 72 % yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 11.58 (s, 1H), 7.38 (d, J=8.2 Hz, 2H), 7.29 (d, J=8.5 Hz, 2H), 7.20 - 7.11 (m, 1H), 7.01 - 6.83 (m, 2H), 6.75 (t, J=7.6 Hz, 1H), 4.39 (s, 1H), 3.87 - 3.65 (m, 4H), 2.60 (br. s., 2H), 2.54 - 2.36 (m, 2H) ppm. Appendix 2. NMR in accordance with Wei-Cheng *et al.* [40]

6.2.4 2-(Morpholino(4-nitrophenyl)methyl)phenol (160)

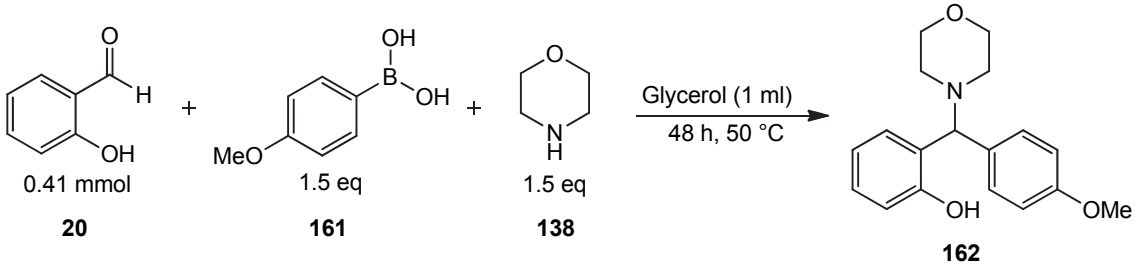


Scheme 58. *The synthesis of 2-(Morpholino(4-nitrophenyl)methyl)phenol* ***160***

4-Nitrophenylboronic acid **159** (0.103 g, 0.615 mmol, 1.5 eq) and 1.0 ml of pure glycerol was added into a test tube with a magnetic stirrer and placed in 50 °C oil bath for 5 minutes until some of the boronic acid had dissolved. Next salicylaldehyde **20** (0.044 ml, 0.41 mmol, 1.0 eq) was added to the reaction mixture and the mixture was left to mix for a couple of minutes. Finally, morpholine **138** (0.054 ml, 0.615 mmol, 1.5 eq) was added to the mixture and left to react in the oil bath. The boronic acid clumped to the bottom of the test tube but it was broken down with a glass rod. The progress of the reaction was monitored by TLC. After 48 hours even though the reaction hadn't finished, it was quenched with 1.0 ml of water and 1.0 ml of saturated $NaHCO_3$ solution. The crude product was extracted with 3-5 x 5ml diethylether until no product could be detected in the extracted organic phase with TLC. The excess solvent was evaporated using rotavapor and the crude product dried in vacuum. The product was purified by flash column chromatography using Hex : EtOAc 7.5 : 2.5 as eluent obtaining the product in 14 % yield. The same procedure was repeated first in 80 °C for 48 hours giving the product in 34 % yield and another time in 80 °C for 72 hours giving the product in 25 % yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 11.29 (br. s., 1H), 8.16 (d, *J*=9.1 Hz, 2H), 7.66 (d, *J*=8.5 Hz, 2H), 7.23 - 7.00 (m, 1H), 6.98 - 6.83 (m, 2H), 6.76 (t, *J*=7.5 Hz, 1H), 4.50 (s, 1H), 3.84 - 3.66 (m, 4H), 2.63 (br. s, 2H), 2.51 - 2.30 (m, 2H); ^{13}C NMR (75MHz, $CDCl_3$) δ = 155.89, 147.04, 129.68, 129.38, 126.45, 124.52, 123.66, 120.32, 117.71, 115.82, 76.43, 66.95, 52.64 ppm. Appendices 3-4

6.2.5 2-((4-Methoxyphenyl)(morpholino)methyl)phenol (162)

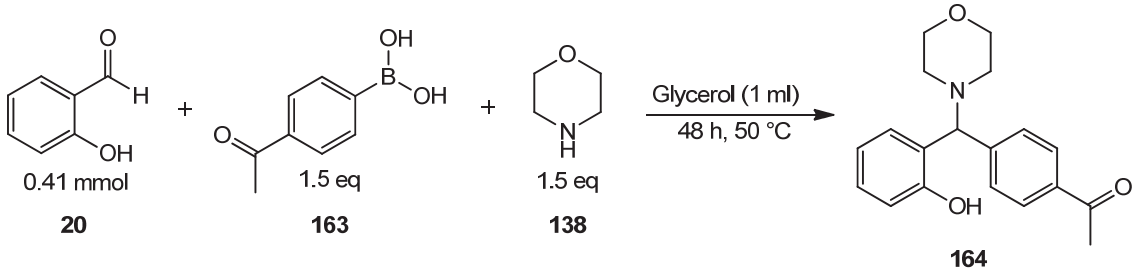


Scheme 59. *The synthesis of 2-((4-Methoxyphenyl)(morpholino)methyl)phenol* ***162***

4-Methoxyphenylboronic acid **161** (0.094 g, 0.615 mmol, 1.5 eq) and 1.0 ml of pure glycerol was added into a test tube with a magnetic stirrer and placed in 50 °C oil bath for 5 minutes until some of the boronic acid had dissolved. Next salicylaldehyde **20** (0.044 ml, 0.41 mmol, 1.0 eq) was added to the reaction mixture and the mixture was left to mix for a couple of minutes. Finally, morpholine **138** (0.054 ml, 0.615 mmol, 1.5 eq) was added to the mixture and left to react in the oil bath while the progress of the reaction was monitored by TLC. After 48 hours the aldehyde spot was observed to be very faint when the reaction was quenched with 1.0 ml of water and 1.0 ml of saturated $NaHCO_3$ solution. The crude product was extracted with 3-5 x 5ml diethylether until no product could be detected in the extracted organic phase with TLC. The excess solvent was evaporated using rotavapor and the crude product dried in vacuum. The product was purified by flash column chromatography using Hex : EtOAc 7.5 : 2.5 as eluent obtaining the product in 72 % yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 11.81 (br. s., 1H), 7.34 (d, *J*=8.5 Hz, 2H), 7.24 - 6.80 (m, 5H), 6.80 - 6.67 (m, 1H), 4.39 (s, 1H), 3.83 - 3.70 (m, 7H), 2.80 - 2.33 (m, 4H) ppm. Appendix 5. NMR in accordance with Gois *et al.* [20]

6.2.6 1-(4-((2-Hydroxyphenyl)(morpholino)methyl)phenyl)ethanone (164)

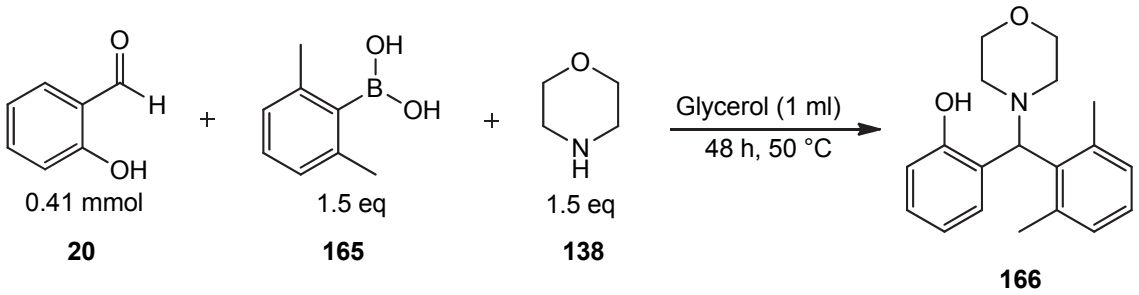


Scheme 60. *The synthesis of 1-(4-((2-Hydroxyphenyl)(morpholino)methyl)phenyl)ethanone* ***164***

4-Acetylphenylboronic acid **163** (0.108 g, 0.615 mmol, 1.5 eq) and 1.0 ml of pure glycerol was added into a test tube with a magnetic stirrer and placed in 50 °C oil bath for 5 minutes until some of the boronic acid had dissolved. Next salicylaldehyde **20** (0.044 ml, 0.41 mmol, 1.0 eq) was added to the reaction mixture and the mixture was left to mix for a couple of minutes. Finally, morpholine **138** (0.054 ml, 0.615 mmol, 1.5 eq) was added to the mixture and left to react in the oil bath while the progress of the reaction was monitored by TLC. After 48 hours the aldehyde spot was observed to be very faint when the reaction was quenched with 1.0 ml of water and 1.0 ml of saturated $NaHCO_3$ solution. The crude product was extracted with 3-5 x 5ml diethylether until no product could be detected in the extracted organic phase with TLC. The excess solvent was evaporated using rotavapor and the crude product dried in vacuum. The product was purified by flash column chromatography using Hex : EtOAc 7 : 3 as eluent obtaining the product in 27 % yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 11.51 (br. s., 1H), 7.90 (d, *J*=8.8 Hz, 2H), 7.55 (d, *J*=8.5 Hz, 2H), 7.21 - 7.07 (m, 1H), 7.00 - 6.82 (m, 2H), 6.79 - 6.68 (m, 1H), 4.46 (s, 1H), 3.87 - 3.66 (m, 4H), 2.56 (s, 5H), 2.52 - 2.40 (m, 2H) ppm. Appendix 6.

6.2.7 2-((2,6-Dimethylphenyl)(morpholino)methyl)phenol (166)

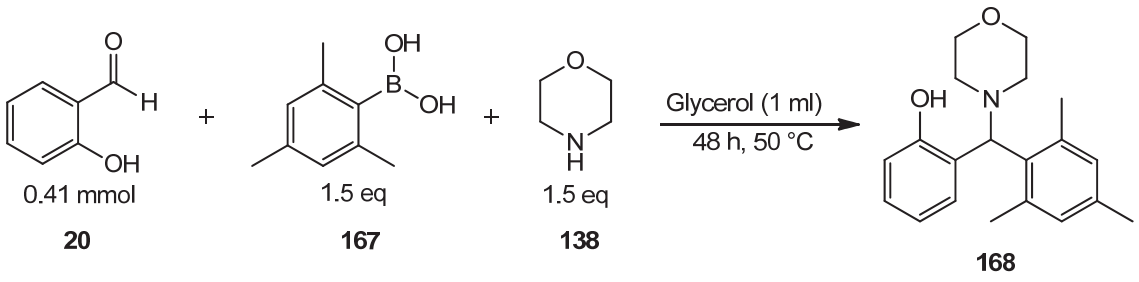


Scheme 61. *The synthesis of 2-((2,6-Dimethylphenyl)(morpholino)methyl)phenol* ***166***

2,6-dimethylphenylboronic acid **165** (0.092 g, 0.615 mmol, 1.5 eq) and 1.0 ml of pure glycerol was added into a test tube with a magnetic stirrer and placed in 50 °C oil bath for 5 minutes until some of the boronic acid had dissolved. Next salicylaldehyde **20** (0.044 ml, 0.41 mmol, 1.0 eq) was added to the reaction mixture and the mixture was left to mix for a couple of minutes. Finally, morpholine **138** (0.054 ml, 0.615 mmol, 1.5 eq) was added to the mixture and left to react in the oil bath while the progress of the reaction was monitored by TLC. After 48 hours even though the reaction hadn't finished, it was quenched with 1.0 ml of water and 1.0 ml of saturated $NaHCO_3$ solution. The crude product was extracted with 3-5 x 5ml diethylether until no product could be detected in the extracted organic phase with TLC. The excess solvent was evaporated using rotavapor and the crude product dried in vacuum. The product was purified by flash column chromatography using Hex : EtOAc 8.5 : 1.5 as eluent obtaining the product in 11 % yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 12.30 (s, 1H), 7.31 - 7.26 (m, 2H), 7.10 - 6.62 (m, 6H), 5.40 (s, 1H), 2.61 - 2.08 (m, 8H), 1.55 (s, 6H) ppm. Appendix 7.

6.2.8 2-(Mesityl(morpholino)methyl)phenol (168)



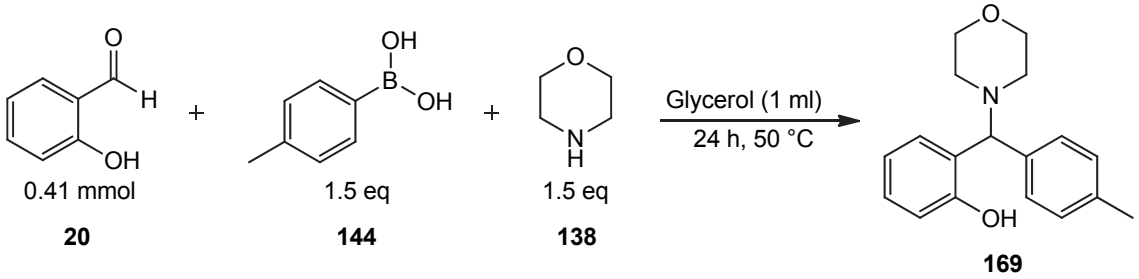
Scheme 62. *The synthesis of 2-(Mesityl(morpholino)methyl)phenol* ***168***

2,4,6-trimethylphenylboronic acid **167** (0.100 g, 0.615 mmol, 1.5 eq) and 1.0 ml of pure glycerol was added into a test tube with a magnetic stirrer and placed in 50 °C oil bath

for 5 minutes until some of the boronic acid had dissolved. Next salicylaldehyde **20** (0.044 ml, 0.41 mmol, 1.0 eq) was added to the reaction mixture and the mixture was left to mix for a couple of minutes. Finally, morpholine **138** (0.054 ml, 0.615 mmol, 1.5 eq) was added to the mixture and left to react in the oil bath while the progress of the reaction was monitored by TLC. After 48 hours even though the reaction hadn't finished, it was quenched with 1.0 ml of water and 1.0 ml of saturated $NaHCO_3$ solution. The crude product was extracted with 3-5 x 5ml diethylether until no product could be detected in the extracted organic phase with TLC. The excess solvent was evaporated using rotavapor and the crude product dried in vacuum. The product was purified by flash column chromatography using Hex : EtOAc 8.5 : 1.5. The product was obtained in 17 % yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 12.24 (s, 1H), 7.06 (ddd, *J*=2.5, 6.3, 8.5 Hz, 1H), 6.97 - 6.54 (m, 5H), 5.35 (s, 1H), 5.30 (s, 1H), 4.08 - 3.73 (m, 3H), 3.61 (br. s., 1H), 3.16 (br. s., 1H), 2.54 (br. s., 5H), 2.24 (s, 7H); ^{13}C NMR (75MHz, $CDCl_3$) δ = 156.91, 137.67, 134.15, 131.26, 129.60, 128.02, 122.55, 119.49, 117.00 (s, 8C), 105.00, 69.78, 20.99 ppm (Carbons missing due to too small sample). Appendices 8, 9.

6.2.9 2-(Morpholino(p-tolyl)methyl)phenol (169)



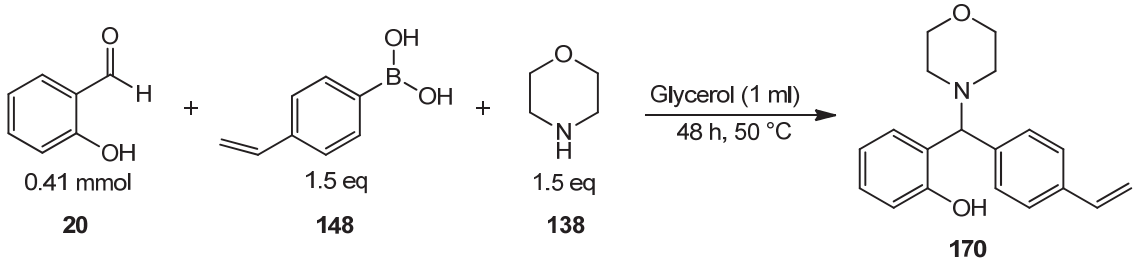
Scheme 63. *The synthesis of 2-(Morpholino(p-tolyl)methyl)phenol* ***169***

p-Tolylboronic acid **144** (0.084 g, 0.615 mmol, 1.5 eq) and 1.0 ml of pure glycerol was added into a test tube with a magnetic stirrer and placed in 50 °C oil bath for 5 minutes until some of the boronic acid had dissolved. Next salicylaldehyde **20** (0.044 ml, 0.41 mmol, 1.0 eq) was added to the reaction mixture and the mixture was left to mix for a couple of minutes. Finally, morpholine **138** (0.054 ml, 0.615 mmol, 1.5 eq) was added to the mixture and left to react in the oil bath while the progress of the reaction was monitored by TLC. After 24 hours the aldehyde spot was gone and so the reaction was quenched with 1.0 ml of water and 1.0 ml of saturated $NaHCO_3$ solution. The crude product was extracted with 3-5 x 5ml diethylether until no product could be detected in the extracted organic phase with TLC. The excess solvent was evaporated using rotavapor and the crude product dried in vacuum. The product was purified by flash column chromatography using Hex : EtOAc 9 : 1 as eluent obtaining the product in 86 % yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 11.76 (s, 1H), 7.31 (d, *J*=7.9 Hz, 2H), 7.21 - 7.04 (m, 3H), 6.93 (d, *J*=7.6 Hz, 1H), 6.86 (d, *J*=8.1 Hz, 1H), 6.72 (t, *J*=7.4 Hz, 1H), 4.38 (s,

1H), 3.82 - 3.72 (m, 4H), 2.85 - 2.37 (m, 4H), 2.30 (s, 3H) ppm. Appendix 10. NMR in accordance with Limin *et al.* [30]

6.2.10 2-(morpholino(4-vinylphenyl)methyl)phenol (170)

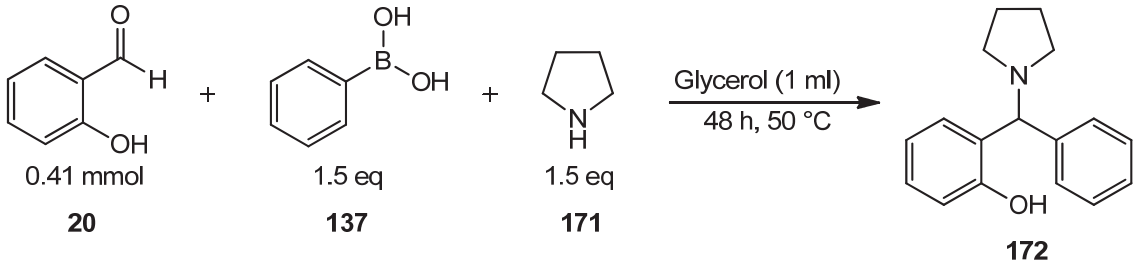


Scheme 64. *The synthesis of 2-(morpholino(4-vinylphenyl)methyl)phenol* ***170***

4-Vinylphenylboronic acid **148** (0.091 g, 0.615 mmol, 1.5 eq) and 1.0 ml of pure glycerol was added into a test tube with a magnetic stirrer and placed in 50 °C oil bath for 5 minutes until some of the boronic acid had dissolved. Next salicylaldehyde **20** (0.044 ml, 0.41 mmol, 1.0 eq) was added to the reaction mixture and the mixture was left to mix for a couple of minutes. Finally, morpholine **138** (0.054 ml, 0.615 mmol, 1.5 eq) was added to the mixture and left to react in the oil bath while the progress of the reaction was monitored by TLC. After 48 hours the aldehyde spot was gone when the reaction was quenched with 1.0 ml of water and 1.0 ml of saturated $NaHCO_3$ solution. The crude product was extracted with 3-5 x 5ml diethylether until no product could be detected in the extracted organic phase with TLC. The excess solvent was evaporated using rotavapor and the crude product dried in vacuum. The product was purified by flash column chromatography using Hex : EtOAc 8 : 2 as eluent obtaining the product in 76 % yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 11.71 (s, 1H), 7.55 - 7.31 (m, 4H), 7.20 - 7.06 (m, 1H), 7.03 - 6.83 (m, 2H), 6.81 - 6.58 (m, 2H), 5.72 (d, *J*=17.6 Hz, 1H), 5.24 (d, *J*=10.8 Hz, 1H), 4.41 (s, 1H), 3.91 - 3.60 (m, 4H), 3.02 - 2.13 (m, 4H); ^{13}C NMR (75MHz, $CDCl_3$) δ = 156.28, 139.03, 137.67, 136.37, 129.56, 128.96, 128.92, 126.98, 124.89, 119.88, 117.29, 114.58, 76.73, 67.13, 52.48 ppm. Appendix 11, 12.

6.2.11 2-(Phenyl(pyrrolidin-1-yl)methyl)phenol (172)

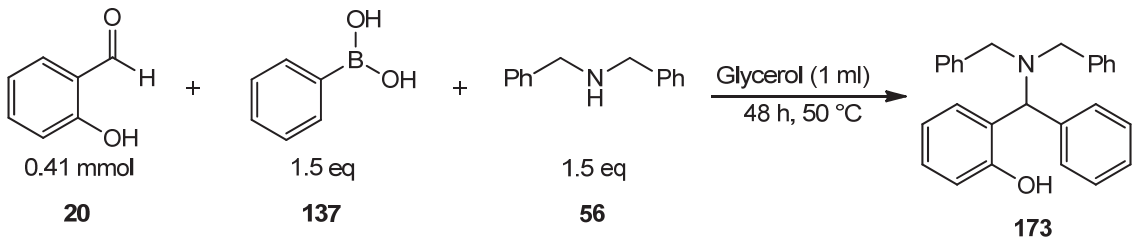


Scheme 65. *The synthesis of 2-(Phenyl(pyrrolidin-1-yl)methyl)phenol* ***172***

Phenylboronic acid **137** (0.075 g, 0.615 mmol, 1.5 eq) and 1.0 ml of pure glycerol was added into a test tube with a magnetic stirrer and placed in 50 °C oil bath for 5 minutes until some of the boronic acid had dissolved. Next salicylaldehyde **20** (0.044 ml, 0.41 mmol, 1.0 eq) was added to the reaction mixture and the mixture was left to mix for a couple of minutes. Finally, pyrrolidine **171** (0.0515 ml, 0.615 mmol, 1.5 eq) was added to the mixture and left to react in the oil bath while the progress of the reaction was monitored by TLC. The oil bath used had to be changed in the beginning of the reaction so the reaction temperature remained under 50 °C for the first 15 - 20 minutes. After 48 hours even though the reaction hadn't finished, it was quenched with 1.0 ml of water and 1.0 ml of saturated $NaHCO_3$ solution. The crude product was extracted with 3-5 x 5ml diethylether until no product could be detected in the extracted organic phase with TLC. The excess solvent was evaporated using rotavapor and the crude product dried in vacuum. The product was purified by flash column chromatography using Hex : EtOAc 9 : 1 as eluent. Two different products were isolated. The yield of the assumed product was 59 %. The same procedure was repeated in 80 °C for 24 hours yielding the product in 44 % yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 12.27 (br. s., 1H), 7.47 (d, *J*=7.3 Hz, 2H), 7.37 - 7.17 (m, 3H), 7.17 - 7.05 (m, 1H), 6.96 (d, *J*=7.6 Hz, 1H), 6.86 (d, *J*=8.2 Hz, 1H), 6.71 (t, *J*=7.3 Hz, 1H), 4.38 (s, 1H), 2.65 (br. s., 2H), 2.51 (br. s., 2H), 1.89 – 1.80 (m, 4H) ppm. Appendix 13. NMR in accordance with Limin *et al.* [30]

6.2.12 2-((Dibenzylamino)(phenyl)methyl)phenol (173)



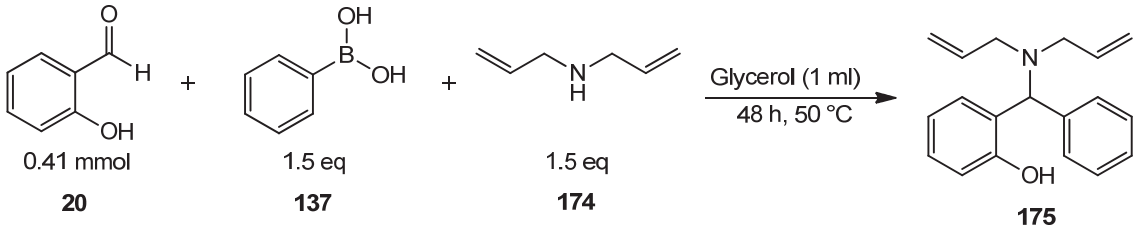
Scheme 66. *The synthesis of 2-((Dibenzylamino)(phenyl)methyl)phenol **173***

Phenylboronic acid **137** (0.075 g, 0.615 mmol, 1.5 eq) and 1.0 ml of pure glycerol was added into a test tube with a magnetic stirrer and placed in 50 °C oil bath for 5 minutes until some of the boronic acid had dissolved. Next salicylaldehyde **20** (0.044 ml, 0.41 mmol, 1.0 eq) was added to the reaction mixture and the mixture was left to mix for a couple of minutes. Finally, dibenzylamine **56** (0.118 ml, 0.615 mmol, 1.5 eq) was added to the mixture and left to react in the oil bath while the progress of the reaction was monitored by TLC. The oil bath used had to be changed in the beginning of the reaction so the reaction temperature remained under 50 °C for the first 15 - 20 minutes. After 48 hours even though the reaction hadn't finished, it was quenched with 1.0 ml of water and 1.0 ml of saturated $NaHCO_3$ solution. The crude product was extracted with 3-5 x 5ml diethylether until no product could be detected in the extracted organic phase with TLC. The excess solvent was evaporated using rotavapor and the crude product dried in

vacuum. The product was purified by flash column chromatography using 2% EtOAc in Hex as eluent obtaining the product in 62 % yield. The same procedure was repeated except that in addition to the 1.5 eq of dibenzylamine added in the beginning of the reaction, another 1.0 eq was added after 24 hours giving the product in 63 % yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 12.12 (s, 1H), 7.49 - 7.28 (m, 15H), 7.19 (t, *J*=7.3 Hz, 1H), 6.96 (d, *J*=7.9 Hz, 1H), 6.83 (d, *J*=7.0 Hz, 1H), 6.72 (t, *J*=7.6 Hz, 1H), 5.16 (s, 1H), 3.97 (d, *J*=13.2 Hz, 2H), 3.42 (d, *J*=13.5 Hz, 2H) ppm. Appendix 14. NMR in accordance with Limin *et al.* [30]

6.2.13 2-((Diallylamino)(phenyl)methyl)phenol (175)

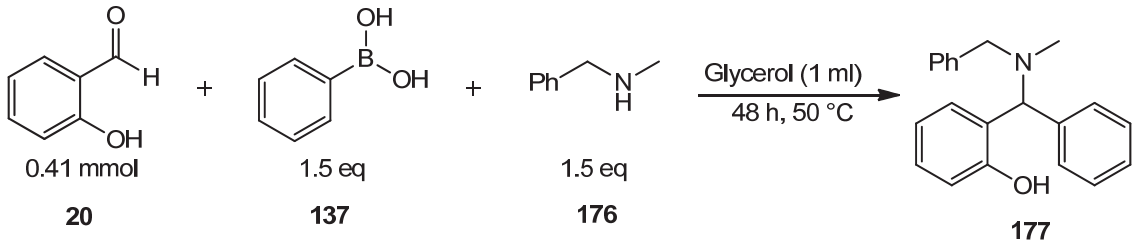


Scheme 67. *The synthesis of 2-((Diallylamino)(phenyl)methyl)phenol* ***175***

Phenylboronic acid **137** (0.075 g, 0.615 mmol, 1.5 eq) and 1.0 ml of pure glycerol was added into a test tube with a magnetic stirrer and placed in 50 °C oil bath for 5 minutes until some of the boronic acid had dissolved. Next salicylaldehyde **20** (0.044 ml, 0.41 mmol, 1.0 eq) was added to the reaction mixture and the mixture was left to mix for a couple of minutes. Finally, diallylamine **174** (0.076 ml, 0.615 mmol, 1.5 eq) was added to the mixture and left to react in the oil bath while the progress of the reaction was monitored by TLC. After 48 hours even though the reaction hadn't finished, it was quenched with 1.0 ml of water and 1.0 ml of saturated $NaHCO_3$ solution. The crude product was extracted with 3-5 x 5ml diethylether until no product could be detected in the extracted organic phase with TLC. The excess solvent was evaporated using rotavapor and the crude product dried in vacuum. The product was purified by flash column chromatography using 2% EtOAc in Hex obtaining the product in 51 % yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 12.13 (s, 1H), 7.53 - 7.21 (m, 5H), 7.20 - 7.04 (m, 1H), 6.97 - 6.75 (m, 2H), 6.75 - 6.57 (m, 1H), 6.09 - 5.72 (m, 2H), 5.32 - 5.09 (m, 4H), 5.06 (s, 1H), 3.42 - 3.34 (m, 2H), 3.07 – 3.00 (m, 2H) ppm. Appendix 15. NMR in accordance with Gois *et al.* [20]

6.2.14 2-((Benzyl(methyl)amino)(phenyl)methyl)phenol (177)

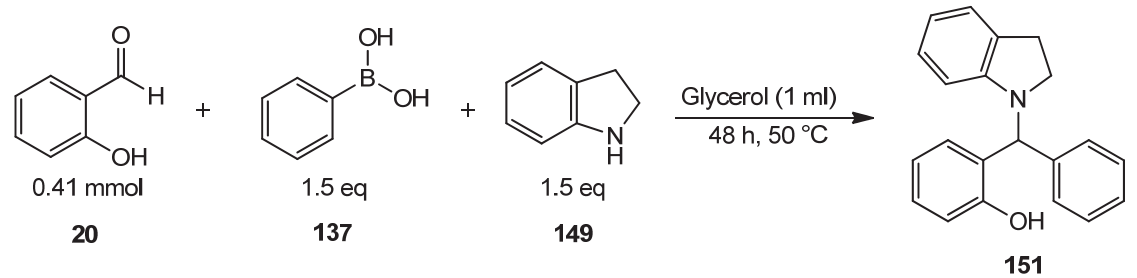


Scheme 68. *The synthesis of 2-((Benzyl(methyl)amino)(phenyl)methyl)phenol* ***177***

Phenylboronic acid **137** (0.075 g, 0.615 mmol, 1.5 eq) and 1.0 ml of pure glycerol was added into a test tube with a magnetic stirrer and placed in 50 °C oil bath for 5 minutes until some of the boronic acid had dissolved. Next salicylaldehyde **20** (0.044 ml, 0.41 mmol, 1.0 eq) was added to the reaction mixture and the mixture was left to mix for a couple of minutes. Finally, *N*-benzylmethylamine **176** (0.0793 ml, 0.615 mmol, 1.5 eq) was added to the mixture and left to react in the oil bath while the progress of the reaction was monitored by TLC. After 48 hours the aldehyde spot was gone when the reaction was quenched with 1.0 ml of water and 1.0 ml of saturated $NaHCO_3$ solution. The crude product was extracted with 3-5 x 5ml diethylether until no product could be detected in the extracted organic phase with TLC. The excess solvent was evaporated using rotavapor and the crude product dried in vacuum. The product was purified by flash column chromatography using 15 % EtOAc in Hex as eluent obtaining the product in 76 % yield. The same procedure was repeated in 80 °C for 24 hours yielding the product in 60 % yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 12.38 (br. s., 1H), 7.50 (d, *J*=7.3 Hz, 2H), 7.42 - 7.28 (m, 8H), 7.16 (t, *J*=7.8 Hz, 1H), 7.00 - 6.89 (m, 2H), 6.74 (t, *J*=7.3 Hz, 1H), 4.73 (s, 1H), 3.58 (br. s., 2H), 2.19 (s, 3H) ppm. Appendix 16. NMR in accordance with Limin *et al.* [30]

6.2.15 2-(Indolin-1-yl(phenyl)methyl)phenol (151)



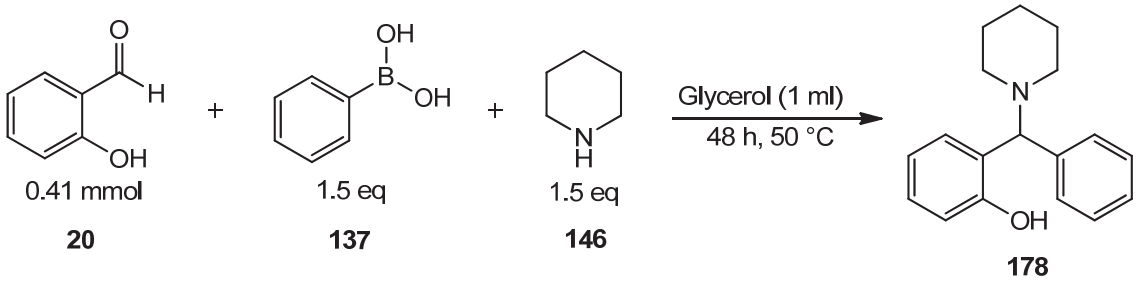
Scheme 69. *The synthesis of 2-(Indolin-1-yl(phenyl)methyl)phenol* ***151***

Phenylboronic acid **137** (0.075 g, 0.615 mmol, 1.5 eq) and 1.0 ml of pure glycerol was added into a test tube with a magnetic stirrer and placed in 50 °C oil bath for 5 minutes until some of the boronic acid had dissolved. Next salicylaldehyde **20** (0.044 ml, 0.41

mmol, 1.0 eq) was added to the reaction mixture and the mixture was left to mix for a couple of minutes. Finally, indoline **149** (0.069 ml, 0.615 mmol, 1.5 eq) was added to the mixture and left to react in the oil bath while the progress of the reaction was monitored by TLC After 48 hours the reaction was completed and it was quenched with 1.0 ml of water and 1.0 ml of saturated $NaHCO_3$ solution. The crude product was extracted with 3-5 x 5ml diethylether until no product could be detected in the extracted organic phase with TLC. The excess solvent was evaporated using rotavapor and the crude product dried in vacuum. The product was purified by flash column chromatography using Hex : EtOAc 9 : 1 as eluent obtaining the product in 94 % yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 10.44 - 9.75 (m, 1H), 7.54 - 7.40 (m, 2H), 7.39 - 7.24 (m, 3H), 7.24 - 7.08 (m, 2H), 7.08 - 6.69 (m, 5H), 6.50 (d, *J*=7.9 Hz, 1H), 5.33 (s, 1H), 3.32 - 3.15 (m, 1H), 3.15 - 2.99 (m, 1H), 2.99 - 2.83 (m, 2H); ^{13}C NMR (75MHz, $CDCl_3$) δ = 156.49, 151.38, 139.84, 132.42, 129.13, 129.08, 129.05, 128.75, 128.31, 127.65, 126.66, 124.89, 121.54, 120.32, 117.30, 112.33, 70.55, 53.79, 28.77 ppm. Appendices 17, 18.

6.2.16 2-(Phenyl(piperidin-1-yl)methyl)phenol (178)



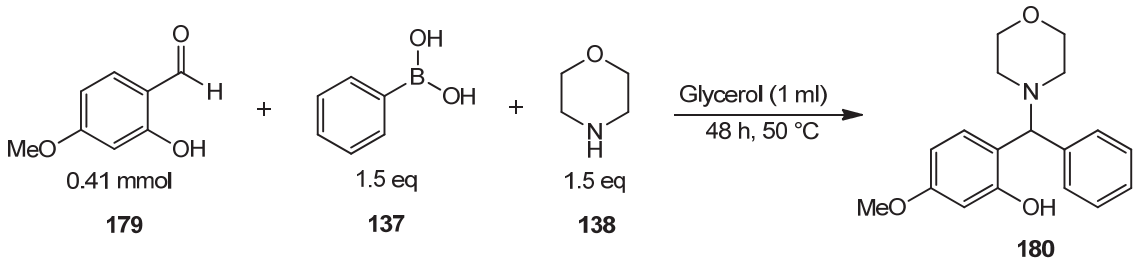
Scheme 70. *The synthesis of 2-(Phenyl(piperidin-1-yl)methyl)phenol* ***178***

Phenylboronic acid **137** (0.075 g, 0.615 mmol, 1.5 eq) and 1.0 ml of pure glycerol was added into a test tube with a magnetic stirrer and placed in 50 °C oil bath for 5 minutes until some of the boronic acid had dissolved. Next salicylaldehyde **20** (0.044 ml, 0.41 mmol, 1.0 eq) was added to the reaction mixture and the mixture was left to mix for a couple of minutes. Finally, piperidine **146** (0.061 ml, 0.615 mmol, 1.5 eq) was added to the mixture and left to react in the oil bath while the progress of the reaction was monitored by TLC. After 48 hours even though the reaction hadn't finished, it was quenched with 1.0 ml of water and 1.0 ml of saturated $NaHCO_3$ solution. The crude product was extracted with 3-5 x 5ml diethylether until no product could be detected in the extracted organic phase with TLC. The excess solvent was evaporated using rotavapor and the crude product dried in vacuum. The product was purified by flash column chromatography using first 10 % EtOAc in Hex and later the eluent was changed to 20 % EtOAc in Hex obtaining the product in 49 % yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 13.02 - 11.99 (m, 1H), 7.40 (d, *J*=6.4 Hz, 2H), 7.36 - 7.19 (m, 3H), 7.18 - 7.04 (m, 1H), 6.94 - 6.82 (m, 2H), 6.69 (t, *J*=7.4 Hz, 1H), 4.48 (s,

1H), 2.42 (br. s., 4H), 1.75 - 1.55 (m, 4H), 1.55 - 1.20 (m, 2H) ppm. Appendix 19. NMR in accordance with Limin *et al.* [30]

6.2.17 5-Methoxy-2-(morpholino(phenyl)methyl)phenol (180)

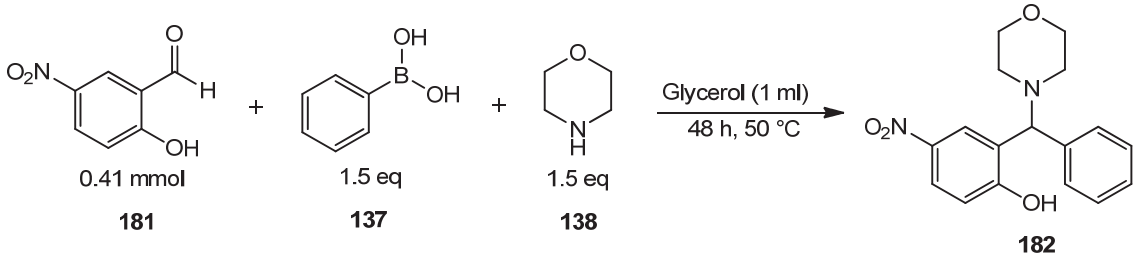


Scheme 71. *The synthesis of 5-Methoxy-2-(morpholino(phenyl)methyl)phenol* ***180***

Phenylboronic acid **137** (0.075 g, 0.615 mmol, 1.5 eq) and 1.0 ml of pure glycerol was added into a test tube with a magnetic stirrer and placed in 50 °C oil bath for 5 minutes until some of the boronic acid had dissolved. Next 2-hydroxy-4-methoxybenzaldehyde **179** (0.062 g, 0.41 mmol, 1.0 eq) was added to the reaction mixture and the mixture was left to mix for a couple of minutes. Finally, morpholine **138** (0.054 ml, 0.615 mmol, 1.5 eq) was added to the mixture and left to react in the oil bath while the progress of the reaction was monitored by TLC. After 48 hours even though the reaction hadn't finished, it was quenched with 1.0 ml of water and 1.0 ml of saturated $NaHCO_3$ solution. The crude product was extracted with 3-5 x 5ml diethylether until no product could be detected in the extracted organic phase with TLC. The excess solvent was evaporated using rotavapor and the crude product dried in vacuum. The product was purified by flash column chromatography using Hex : EtOAc 7.5 : 2.5 as eluent obtaining the product in 58 % yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 11.85 (br. s., 1H), 7.45 - 7.35 (m, 2H), 7.35 - 7.21 (m, 3H), 6.82 (d, *J*=8.5 Hz, 1H), 6.43 (d, *J*=2.6 Hz, 1H), 6.30 (dd, *J*=2.5, 8.3 Hz, 1H), 4.38 (s, 1H), 3.74 (s, 7H), 2.60 - 2.40 (m, 4H) ppm. Appendix 20. NMR in accordance with Gois *et al.* [20]

6.2.18 2-(Morpholino(phenyl)methyl)-4-nitrophenol (182)

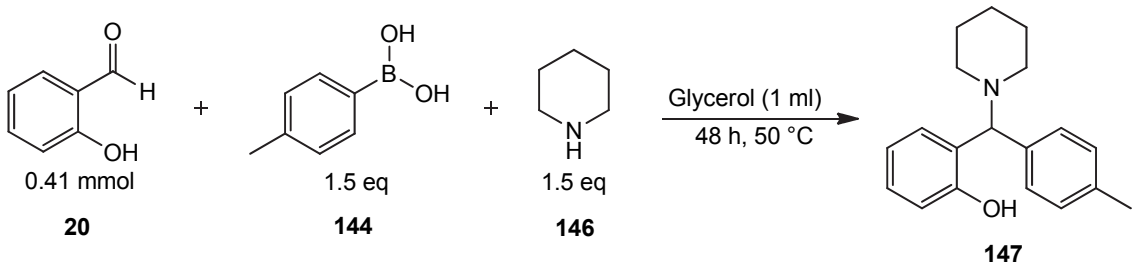


Scheme 72. *The synthesis of 2-(Morpholino(phenyl)methyl)-4-nitrophenol* ***182***

Phenylboronic acid **137** (0.075 g, 0.615 mmol, 1.5 eq) and 1.0 ml of pure glycerol was added into a test tube with a magnetic stirrer and placed in 50 °C oil bath for 5 minutes until some of the boronic acid had dissolved. Next 2-hydroxy-5-nitrobenzaldehyde **181** (0.069 ml, 0.41 mmol, 1.0 eq) was added to the reaction mixture and the mixture was left to mix for a couple of minutes. Finally, morpholine **138** (0.054 ml, 0.615 mmol, 1.5 eq) was added to the mixture and left to react in the oil bath while the progress of the reaction was monitored by TLC. After 48 hours even though the reaction hadn't finished, it was quenched with 1.0 ml of water and 1.0 ml of saturated $NaHCO_3$ solution. The forming product could not be detected on TLC plates because it precipitated from the reaction mixture. After 48 hours the reaction was quenched with 1 ml H_2O and 1 ml of $NaHCO_3$ and the crude product was extracted with 3-5 x 5ml EtOAc instead of diethylether until no product could be detected in the extracted organic phase with TLC. The excess solvent was evaporated using rotavapor and the crude product dried in vacuum. The product was purified by flash column chromatography using Hex : EtOAc 8 : 2 as eluent obtaining the product in 66 % yield. The product was still contaminated with boronic acid.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 13.20 (br. s., 1H), 8.29 - 8.17 (m, 1H), 8.05 (dd, *J*=2.6, 9.1 Hz, 1H), 7.91 (d, *J*=2.6 Hz, 1H), 7.65 - 7.30 (m, 6H), 6.92 (d, *J*=8.8 Hz, 1H), 4.55 (s, 1H), 3.77 (br. s., 4H), 3.15 - 2.16 (m, 4H); ^{13}C NMR (75MHz, $CDCl_3$) δ = 141.03 - 140.18, 137.56, 135.74, 133.11 - 132.35, 129.56, 129.16, 128.72 - 128.49, 128.19, 126.03, 125.40, 125.22, 117.84, 76.31, 66.84, 53.26 - 51.30 ppm. Appendices 21, 22.

6.2.19 2-(Piperidin-1-yl(p-tolyl)methyl)phenol (147)



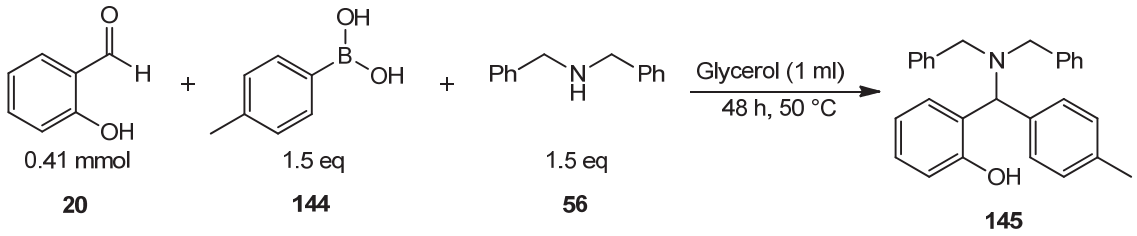
Scheme 73. *The synthesis of 2-(Piperidin-1-yl(p-tolyl)methyl)phenol* ***147***

p-Tolylboronic acid **144** (0.084 g, 0.615 mmol, 1.5 eq) and 1.0 ml of pure glycerol was added into a test tube with a magnetic stirrer and placed in 50 °C oil bath for 5 minutes until some of the boronic acid had dissolved. Next salicylaldehyde **20** (0.044 ml, 0.41 mmol, 1.0 eq) was added to the reaction mixture and the mixture was left to mix for a couple of minutes. Finally, piperidine **146** (0.061 ml, 0.615 mmol, 1.5 eq) was added to the mixture and left to react in the oil bath while the progress of the reaction was monitored by TLC. After 48 hours even though the reaction hadn't finished, it was quenched with 1.0 ml of water and 1.0 ml of saturated $NaHCO_3$ solution. The crude product was extracted with 3-5 x 5ml diethylether until no product could be detected in the extracted

organic phase with TLC. The excess solvent was evaporated using rotavapor and the crude product dried in vacuum. The product was purified by flash column chromatography using first 4 % EtOAc in Hex as eluent and later 8:2 EtOAc in Hex with a couple of drops of Et_3N to prevent the product dragging inside the column. The product was obtained in 69 % yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 12.63 (br. s., 1H), 7.39 - 7.20 (m, 2H), 7.20 - 7.05 (m, 3H), 6.88 (t, *J*=8.2 Hz, 2H), 6.69 (t, *J*=7.6 Hz, 1H), 4.47 (s, 1H), 2.43 (br. s., 4H), 2.33 (s, 3H), 1.67 - 1.56 (m, 4H), 1.57 - 1.38 (m, 2H) ppm. Appendix 23. NMR in accordance with Gois *et al.* [20]

6.2.20 2-((Dibenzylamino)(p-tolyl)methyl)phenol (145)

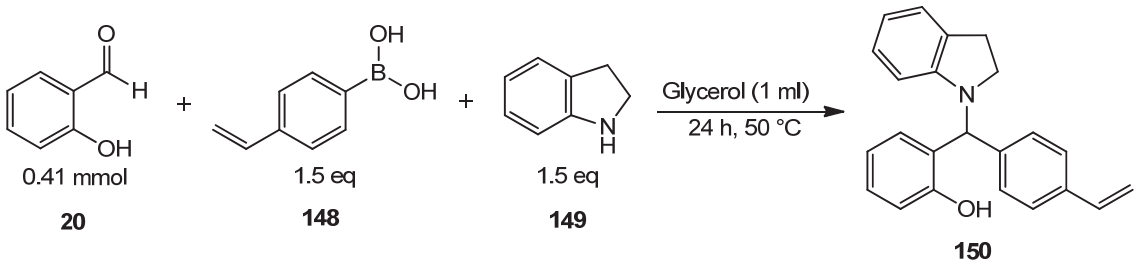


Scheme 74. *The synthesis of 2-((Dibenzylamino)(p-tolyl)methyl)phenol* ***145***

p-Tolylboronic acid **144** (0.084 g, 0.615 mmol, 1.5 eq) and 1.0 ml of pure glycerol was added into a test tube with a magnetic stirrer and placed in 50 °C oil bath for 5 minutes until some of the boronic acid had dissolved. Next salicylaldehyde **20** (0.044 ml, 0.41 mmol, 1.0 eq) was added to the reaction mixture and the mixture was left to mix for a couple of minutes. Finally, dibenzylamine **56** (0.118 ml, 0.615 mmol, 1.5 eq) was added to the mixture and left to react in the oil bath while the progress of the reaction was monitored by TLC. After 48 hours even though the reaction hadn't finished, it was quenched with 1.0 ml of water and 1.0 ml of saturated $NaHCO_3$ solution. The crude product was extracted with 3-5 x 5ml diethylether until no product could be detected in the extracted organic phase with TLC. The excess solvent was evaporated using rotavapor and the crude product dried in vacuum. The product was purified by flash column chromatography using first 4 % EtOAc in Hex and later 8:2 EtOAc in Hex obtaining the product in 74 % yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 12.19 (s, 1H), 7.44 - 7.13 (m, 15H), 6.95 (d, *J*=8.1 Hz, 1H), 6.83 (d, *J*=7.6 Hz, 1H), 6.71 (t, *J*=7.6 Hz, 1H), 5.13 (s, 1H), 3.96 (d, *J*=13.2 Hz, 2H), 3.40 (d, *J*=13.2 Hz, 2H), 2.42 (s, 3H) ppm. Appendix 24. NMR in accordance with Gois *et al.* [20]

6.2.21 2-(Indolin-1-yl(4-vinylphenyl)methyl)phenol (150)

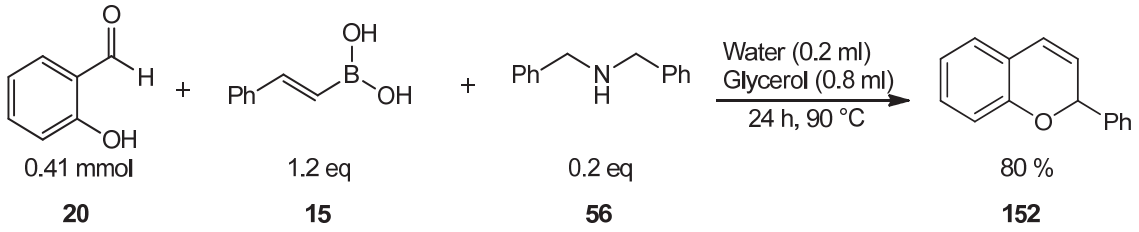


Scheme 75. *The synthesis of 2-(Indolin-1-yl(4-vinylphenyl)methyl)phenol* ***150***

4-Vinylboronic acid **148** (0.091 g, 0.615 mmol, 1.5 eq) and 1.0 ml of pure glycerol was added into a test tube with a magnetic stirrer and placed in 50 °C oil bath for 5 minutes until some of the boronic acid had dissolved. Next salicylaldehyde **20** (0.044 ml, 0.41 mmol, 1.0 eq) was added to the reaction mixture and the mixture was left to mix for a couple of minutes. Finally, indoline **149** (0.069 ml, 0.615 mmol, 1.5 eq) was added to the mixture and left to react in the oil bath while the progress of the reaction was monitored by TLC After 24 hours the reaction was finished and it was quenched with 1.0 ml of water and 1.0 ml of saturated $NaHCO_3$ solution. The crude product was extracted with 3-5 x 5ml diethylether until no product could be detected in the extracted organic phase with TLC. The excess solvent was evaporated using rotavapor and the crude product dried in vacuum. The product was purified by flash column chromatography using 9:1 EtOAc in Hex as eluent. A tiny fraction was lost due to product dragging in the column but the overall yield was still 99 %.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 10.46 - 9.71 (m, 1H), 7.59 - 7.34 (m, 4H), 7.33 - 7.14 (m, 2H), 7.13 - 6.83 (m, 5H), 6.75 (dd, *J*=11.0, 17.7 Hz, 1H), 6.57 (d, *J*=7.6 Hz, 1H), 5.80 (dd, *J*=0.9, 17.6 Hz, 1H), 5.39 (s, 1H), 5.31 (dd, *J*=0.9, 10.8 Hz, 1H), 3.36 - 3.22 (m, 1H), 3.14 (m, 1H), 3.06 - 2.84 (m, 2H); ^{13}C NMR (75MHz, $CDCl_3$) δ = 156.49, 151.36, 139.35, 137.59, 136.50, 132.43, 129.34, 129.16, 128.75, 127.69, 126.90, 126.56, 124.94, 121.56, 120.38, 117.33, 114.65, 112.34, 70.08, 66.18, 53.75, 28.80, 15.61 ppm. Appendices 25, 26.

6.2.22 2-phenyl-2*H*-chromene (152)



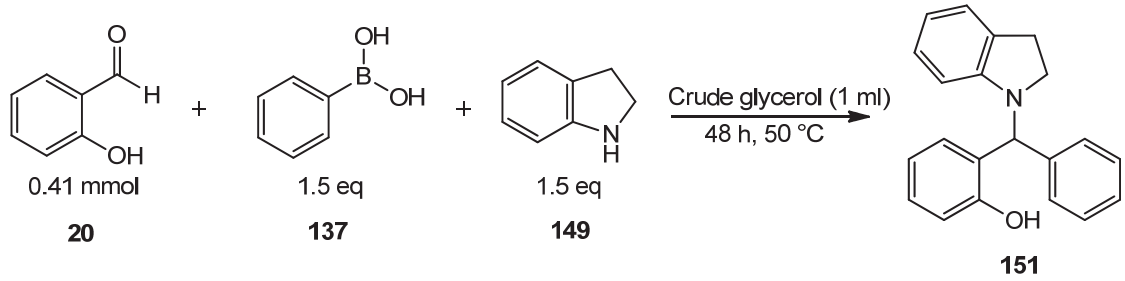
Scheme 76. *The synthesis of 2-phenyl-2H-chromene* ***152***

Phenylvinylboronic acid **15** (0.073 g, 0.492 mmol, 1.2 eq), 0.2 ml of water and 0.8 ml of pure glycerol was added into a test tube with a magnetic stirrer and placed in 90 °C

oil bath for 5 minutes until some of the boronic acid had dissolved. Next salicylaldehyde **20** (0.044 ml, 0.41 mmol, 1.0 eq) was added to the reaction mixture and the mixture was left to mix for a couple of minutes. Finally, dibenzylamine **56** (0.016 ml, 0.082 mmol, 0.2 eq) was added to the mixture and left to react in the oil bath while the progress of the reaction was monitored by TLC. After 24 hours the reaction had finished and it was quenched with 1.0 ml of water and 1.0 ml of saturated $NaHCO_3$ solution. The crude product was extracted with 3-5 x 5ml diethylether until no product could be detected in the extracted organic phase with TLC. The excess solvent was evaporated using rotavapor and the crude product dried in vacuum. The product was purified by flash column chromatography using 4 % EtOAc in Hex obtaining the product in 80 % yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.53 - 7.43 (m, 2H), 7.43 - 7.29 (m, 3H), 7.26 (s, 1H), 7.12 (dt, *J*=1.8, 7.6 Hz, 1H), 7.02 (dd, *J*=1.6, 7.5 Hz, 1H), 6.93 - 6.83 (m, 1H), 6.80 (d, *J*=8.2 Hz, 1H), 6.54 (dd, *J*=1.8, 10.0 Hz, 1H), 5.93 (dd, *J*=2.1, 3.2 Hz, 1H), 5.81 (dd, *J*=3.4, 9.8 Hz, 1H) ppm. Appendix 27. NMR in accordance with Wang *et al.* [29]

6.2.23 2-(Indolin-1-yl(phenyl)methyl)phenol (151) in crude glycerol



Scheme 77. *The synthesis of 2-(Indolin-1-yl(phenyl)methyl)phenol* ***151*** *in crude glycerol.*

Phenylboronic acid **137** (0.075 g, 0.615 mmol, 1.5 eq) and 1.0 ml of crude glycerol was added into a test tube with a magnetic stirrer and placed in 50 °C oil bath for 5 minutes until some of the boronic acid had dissolved. Next salicylaldehyde **20** (0.044 ml, 0.41 mmol, 1.0 eq) was added to the reaction mixture and the mixture was left to mix for a couple of minutes. Finally, indoline **149** (0.069 ml, 0.615 mmol, 1.5 eq) was added to the mixture and left to react in the oil bath while the progress of the reaction was monitored by TLC. After 48 hours, even though the reaction wasn't completed it was quenched with 1.0 ml of water and 1.0 ml of saturated $NaHCO_3$ solution. The mixture turned very viscous so about 5 ml of water was added for the extraction process. The crude product was extracted with 5-7 x 5ml diethylether until no product could be detected in the extracted organic phase with TLC. The excess solvent was evaporated using rotavapor and the crude product dried in vacuum. The product was purified by flash column chromatography using Hex : EtOAc 9 : 1 as eluent obtaining the product in 84 % yield.

^{1}H & ^{13}C NMR with the same spectral characterization as before.

7. REFERENCES

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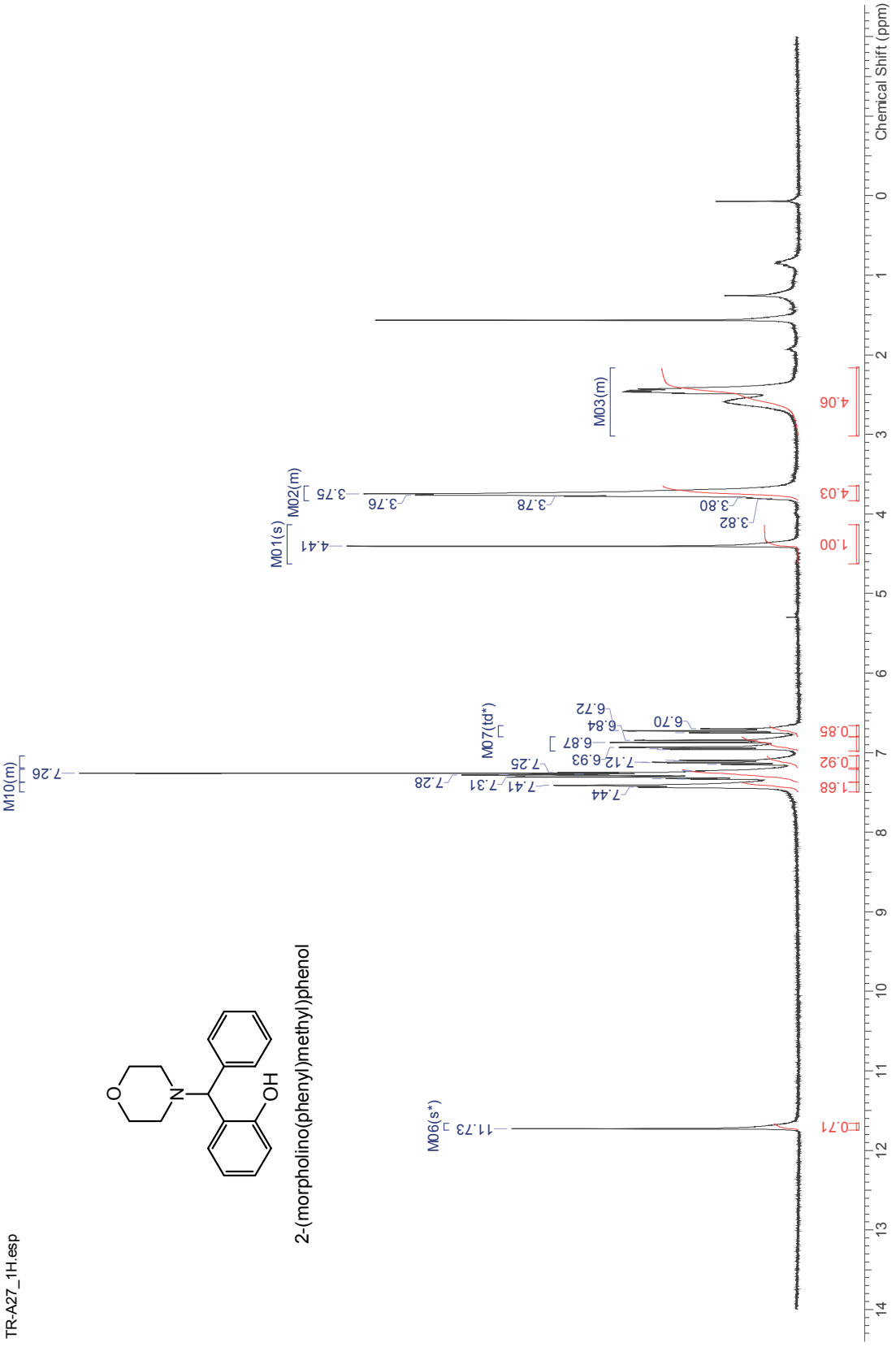
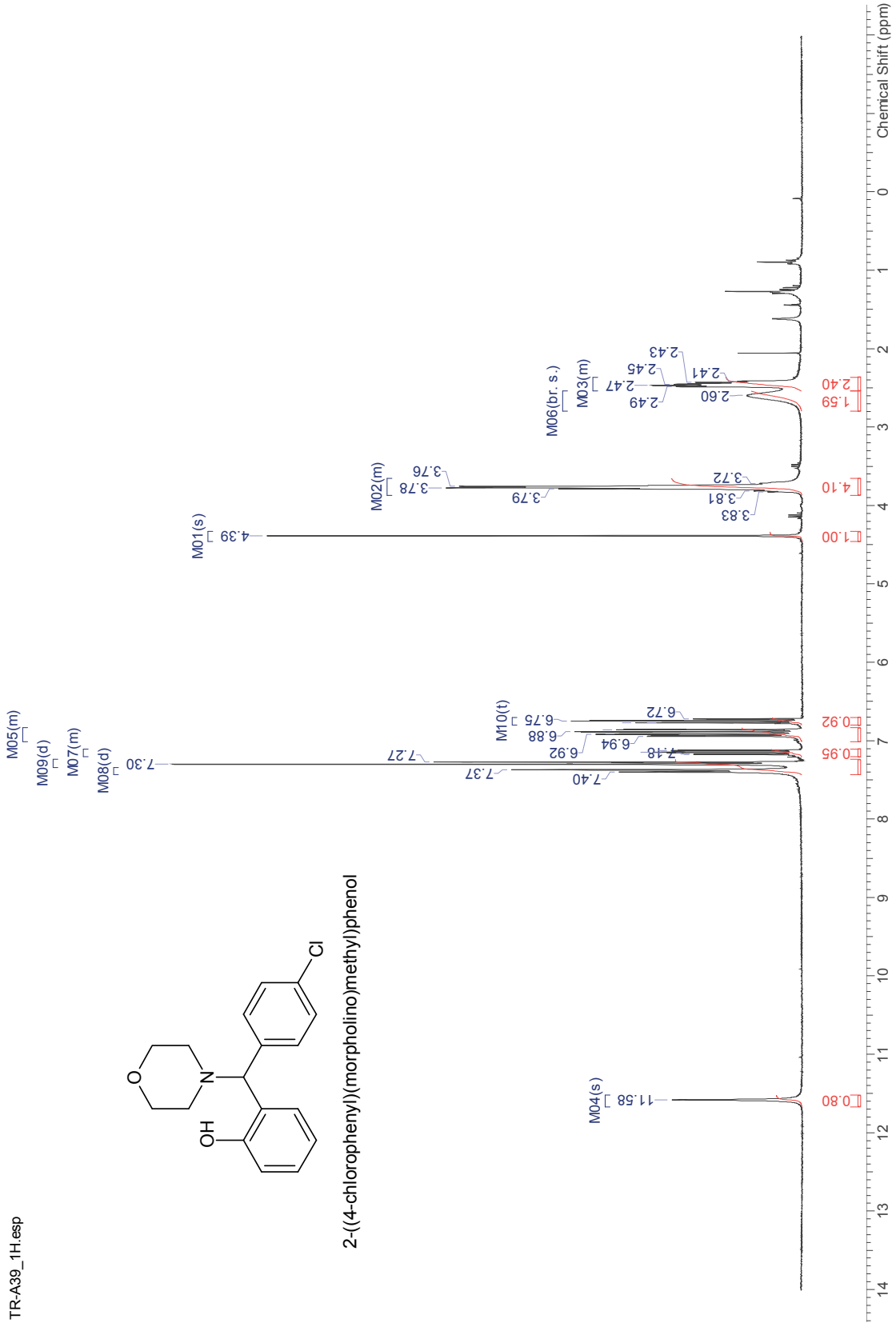
8. APPENDICES

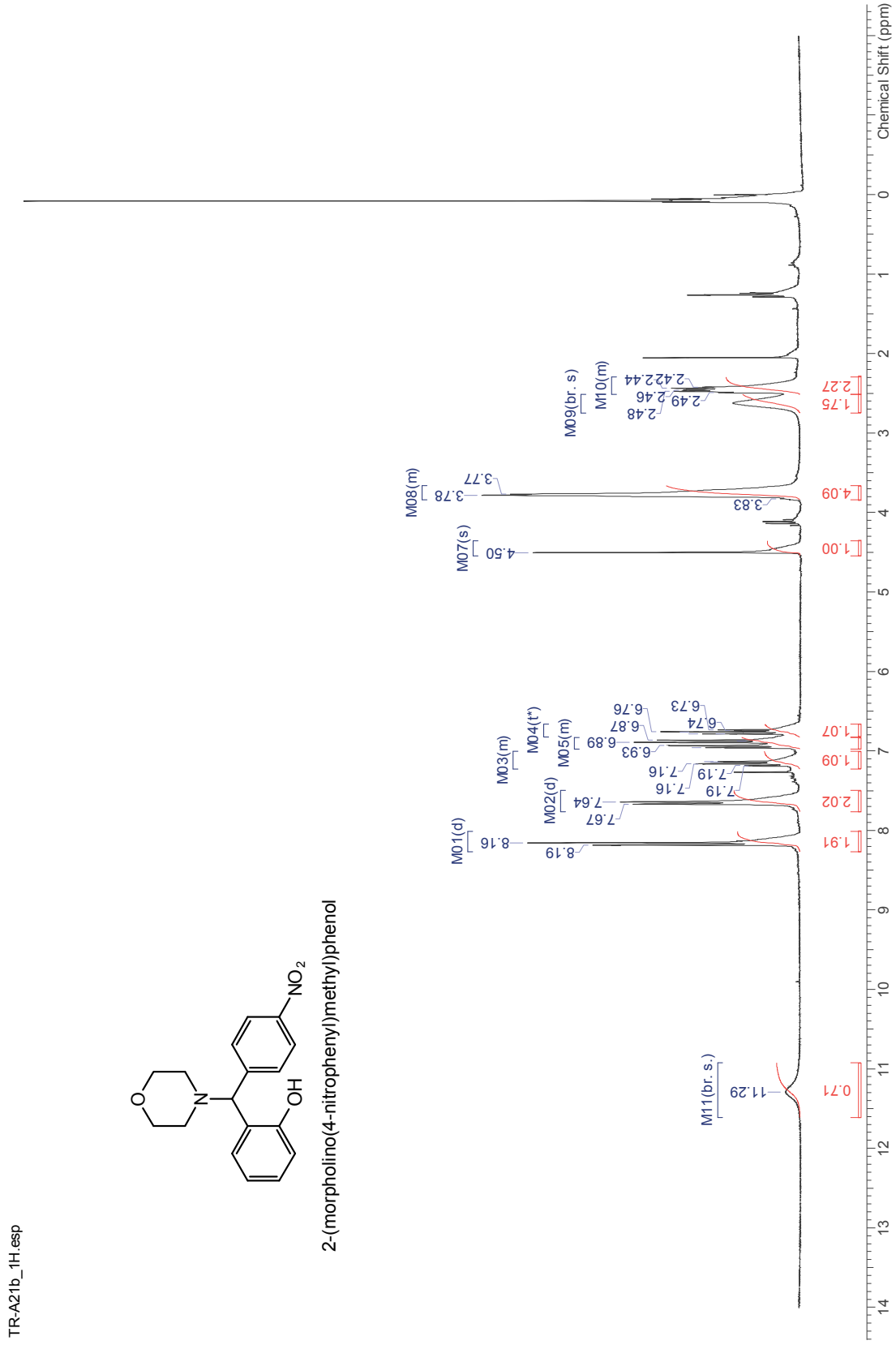
Appendix 1. ^{1}H NMR for compound 139



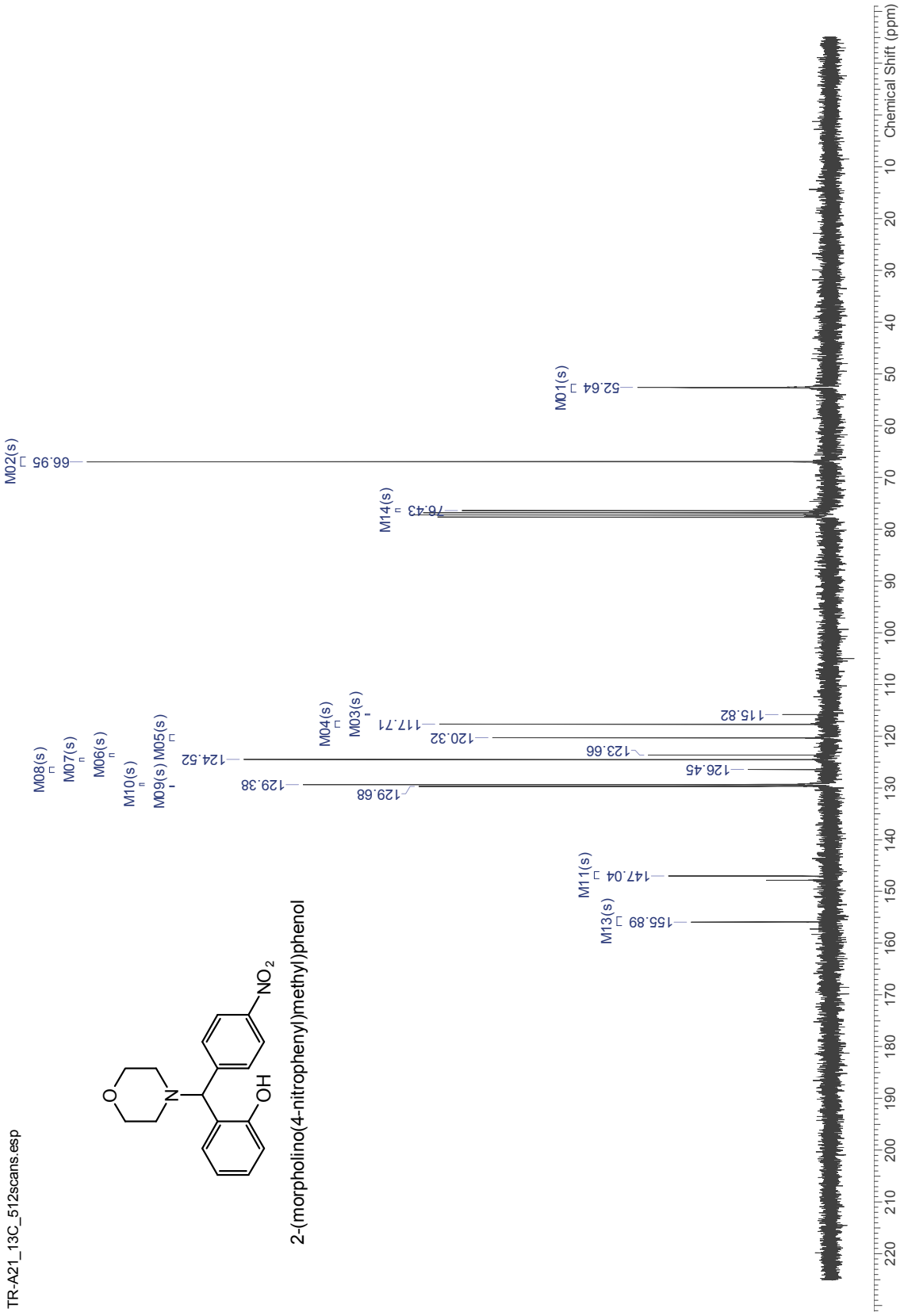
Appendix 2. ^{1}H NMR for compound 158



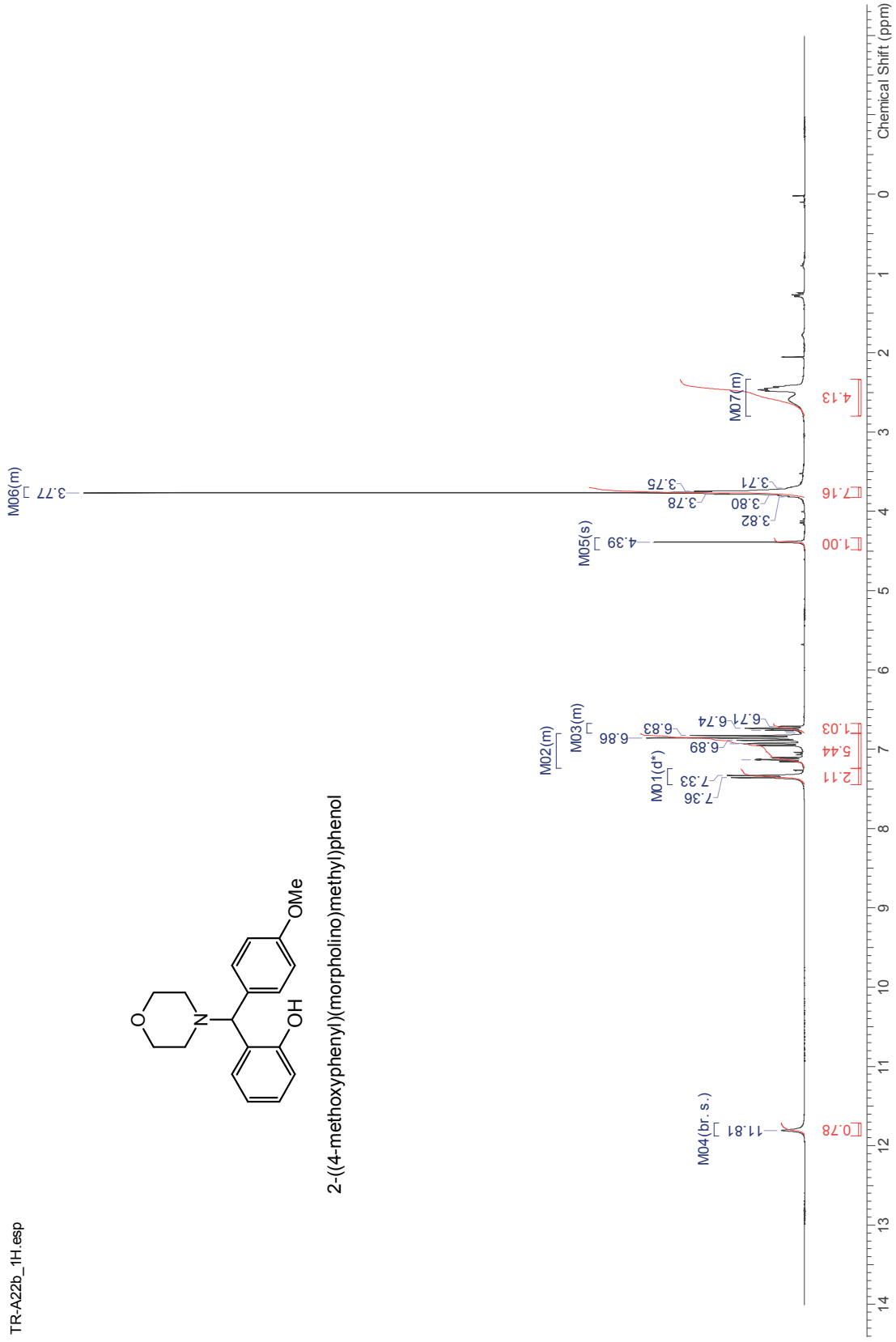
Appendix 3. ^{1}H NMR for compound 160



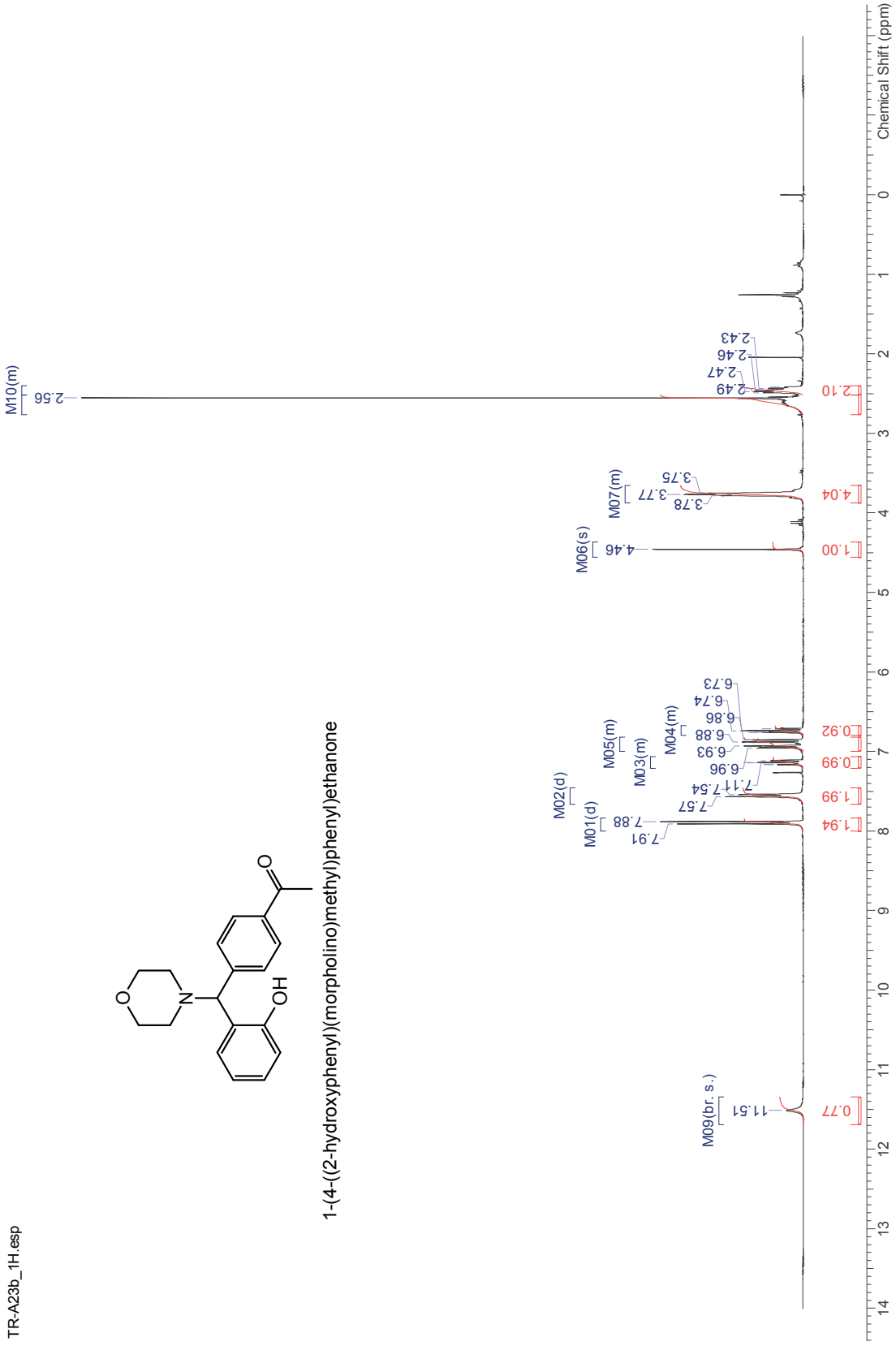
Appendix 4. ^{13}C NMR for compound 160



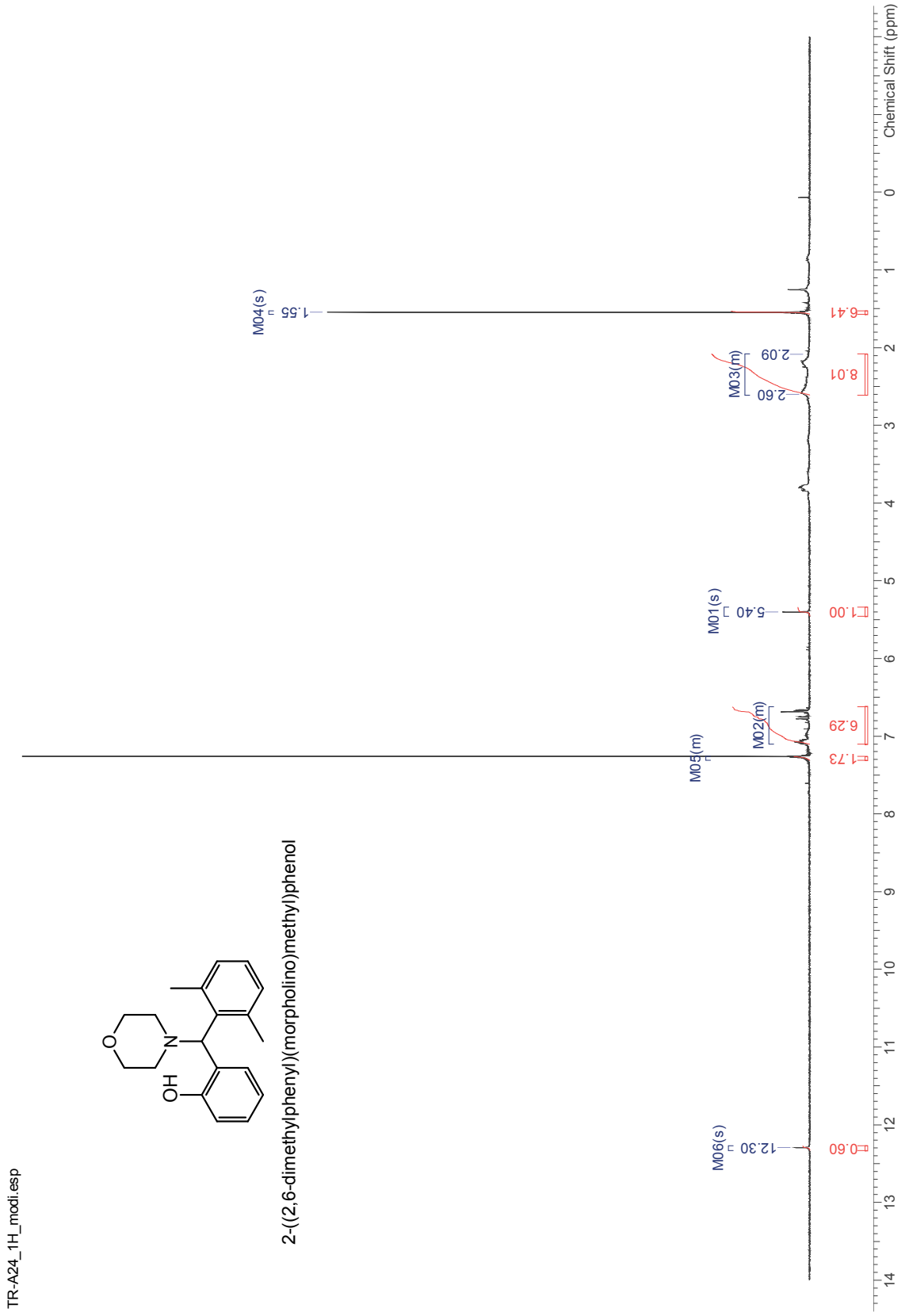
Appendix 5. ^{1}H NMR for compound 162



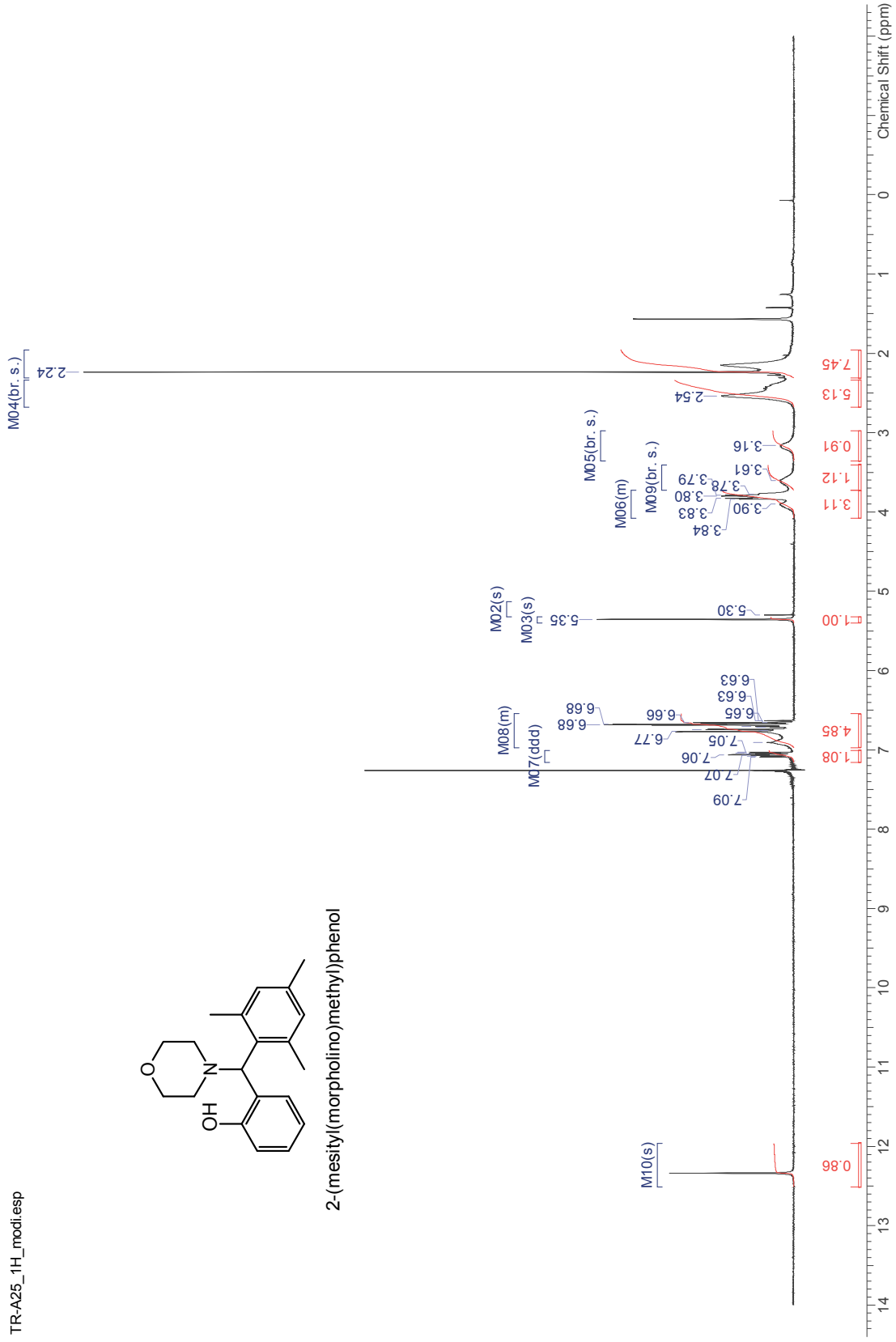
Appendix 6. ^{1}H NMR for compound 164



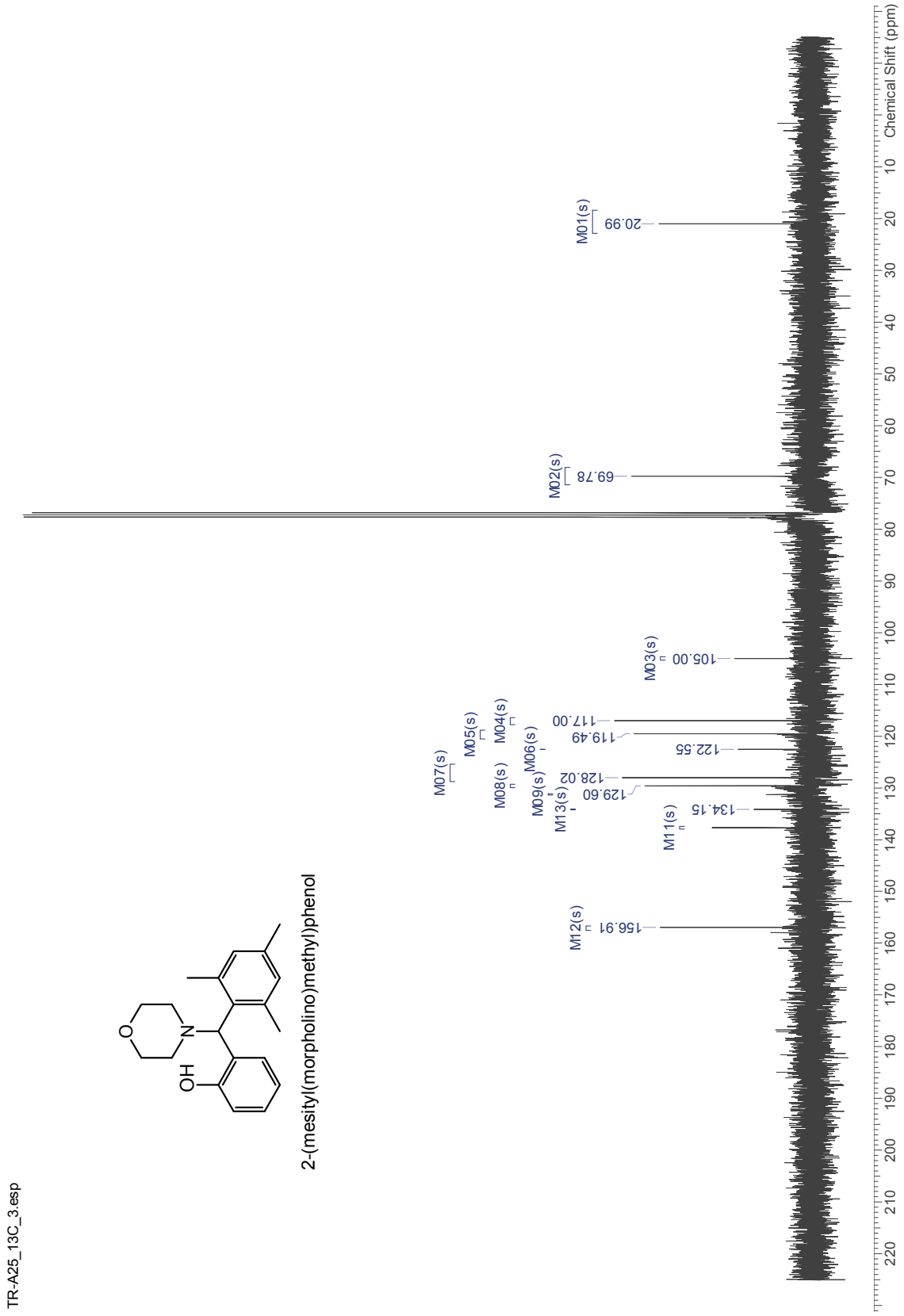
Appendix 7. ^{1}H NMR for compound 166



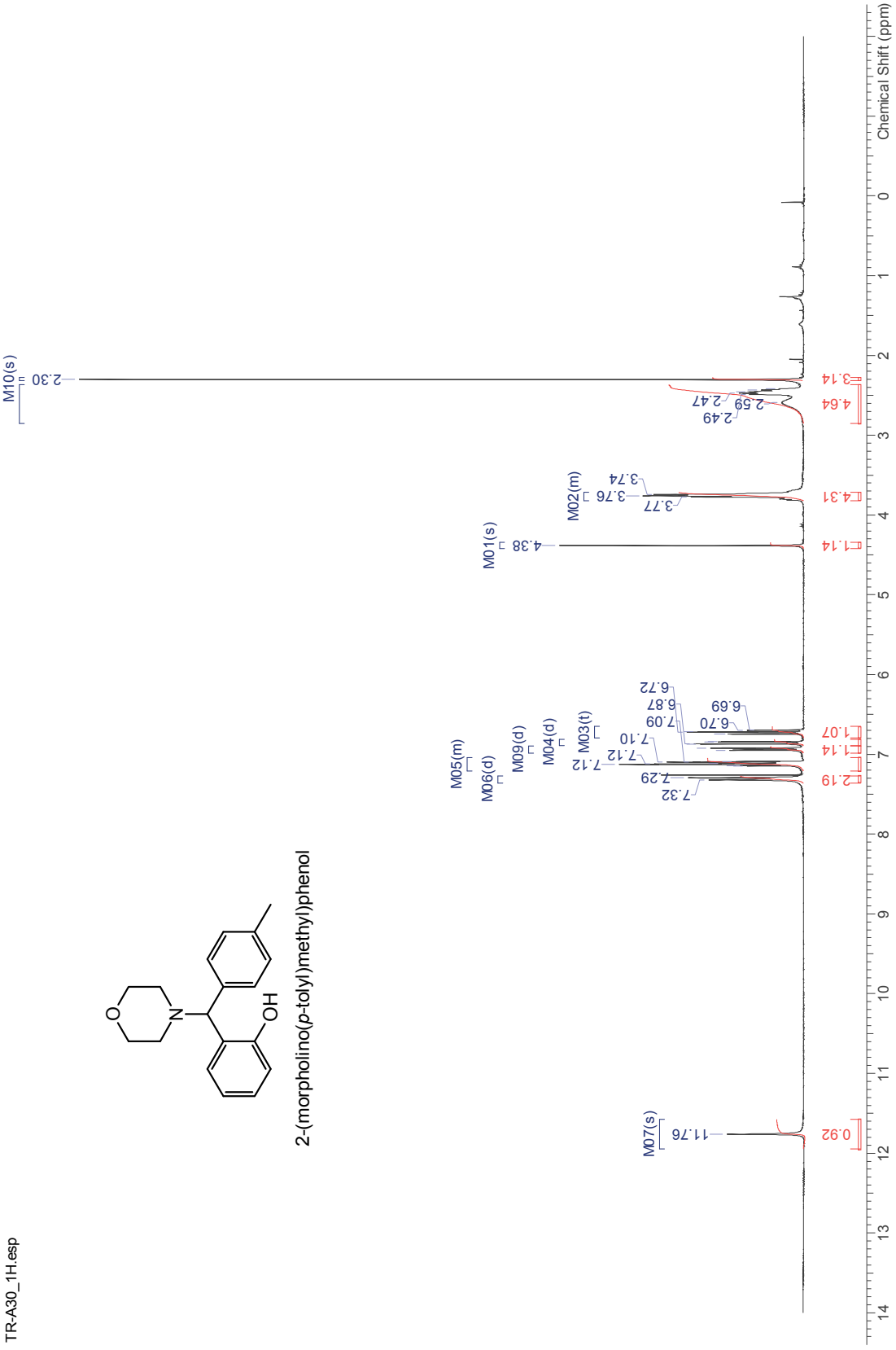
Appendix 8. ^{1}H NMR for compound 168



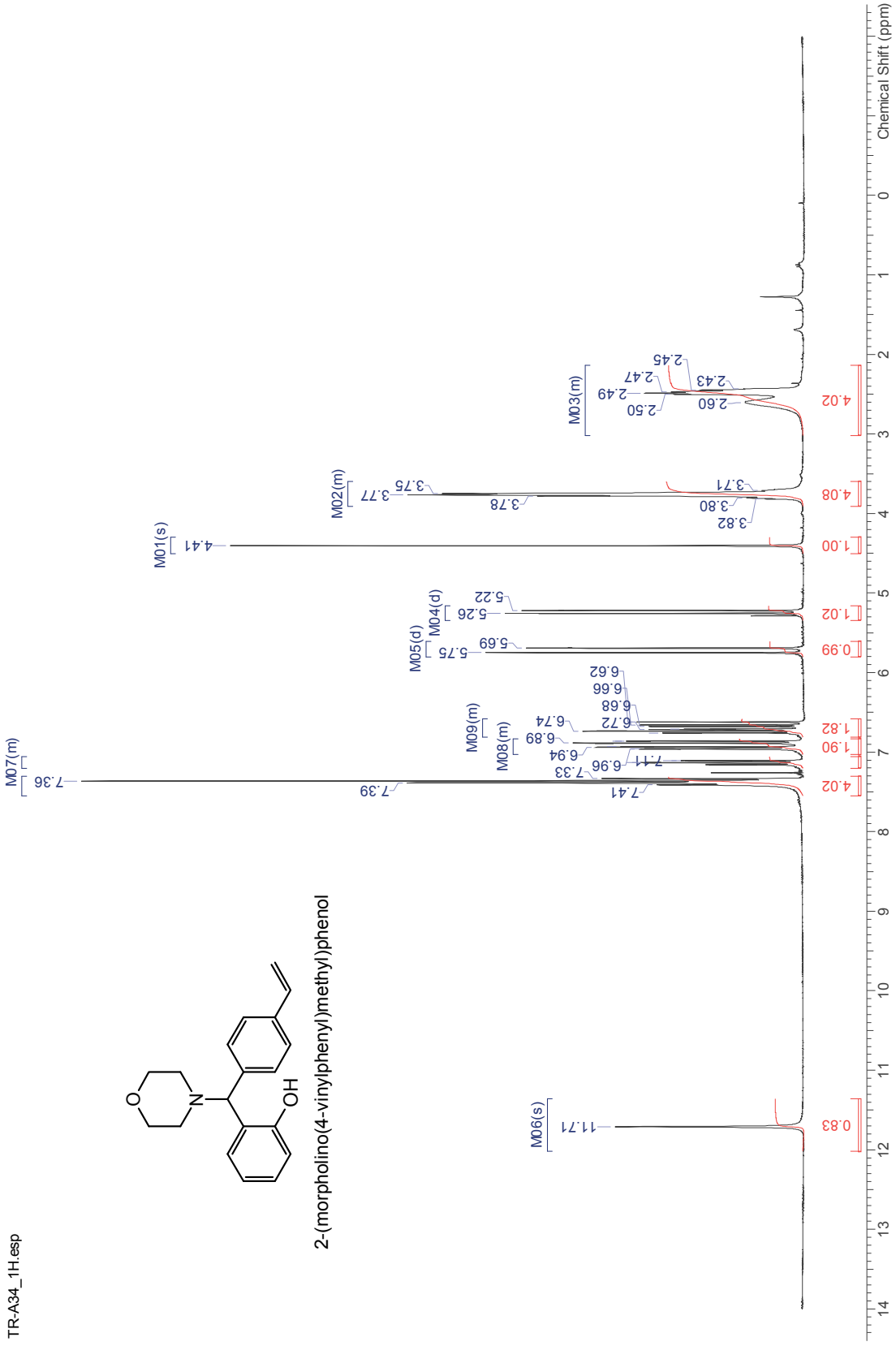
Appendix 9. ^{13}C NMR for compound 168



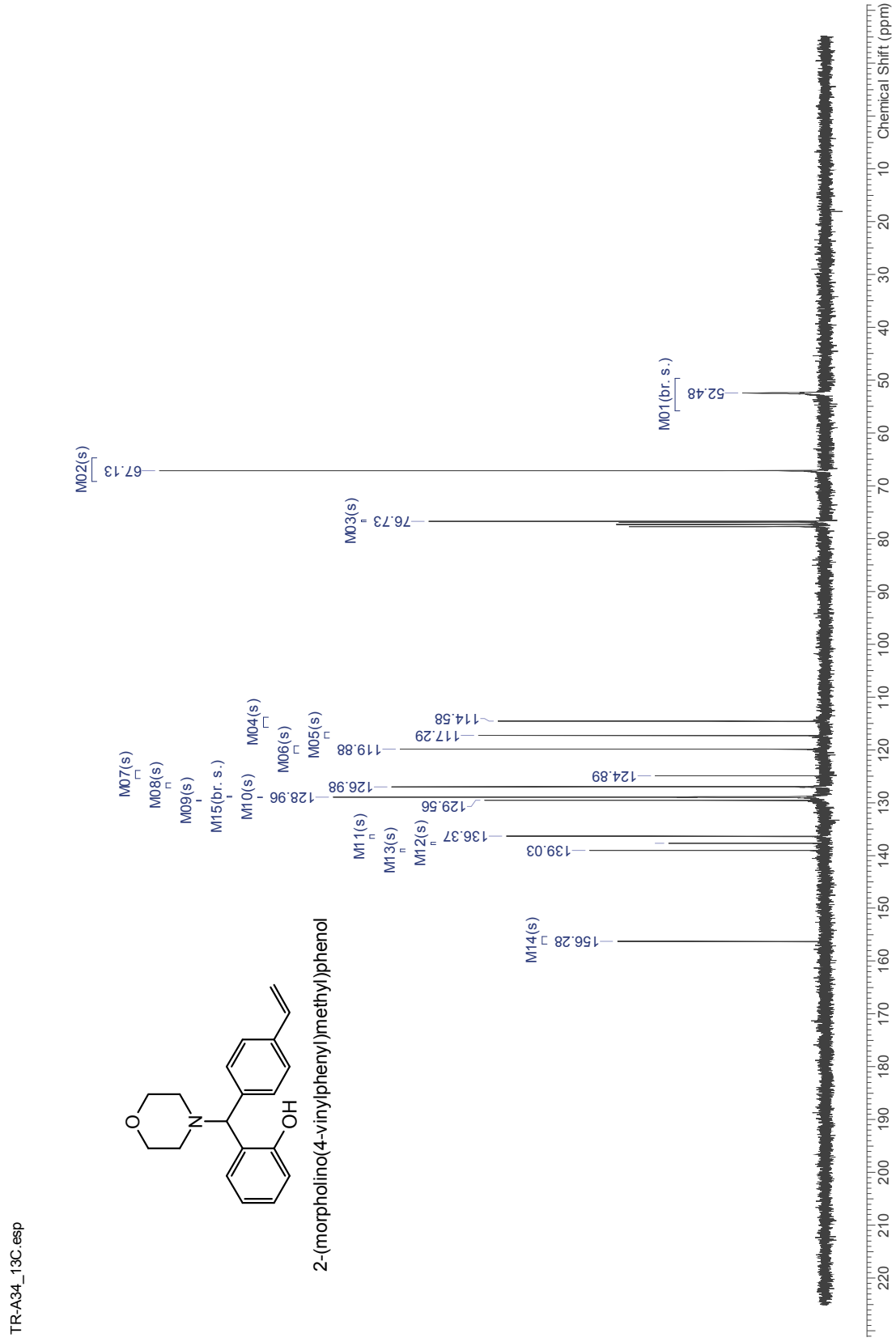
Appendix 10. ^{1}H NMR for compound 169



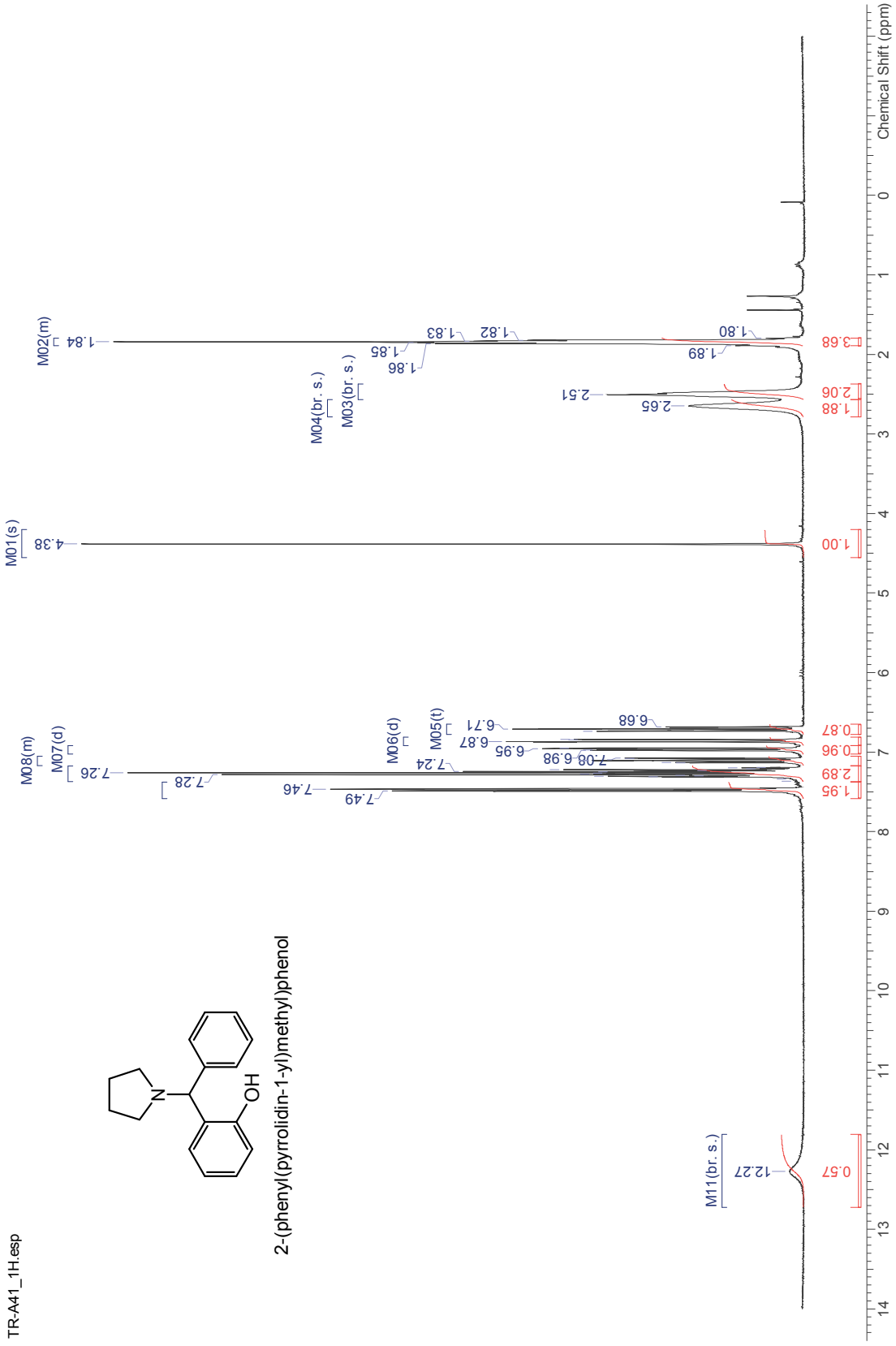
Appendix 11. ^{1}H NMR for compound 170



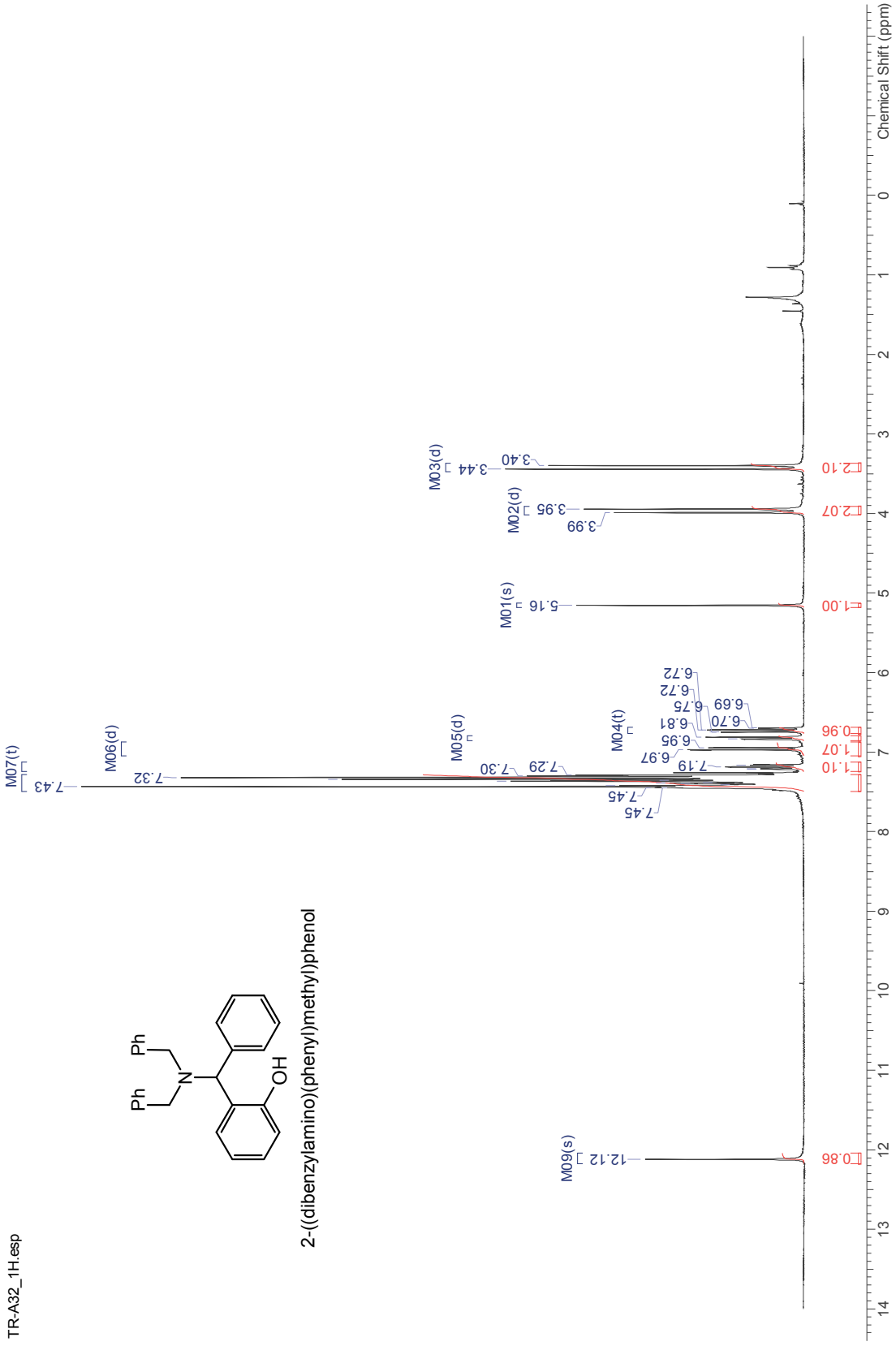
Appendix 12. ^{13}C NMR for compound 170



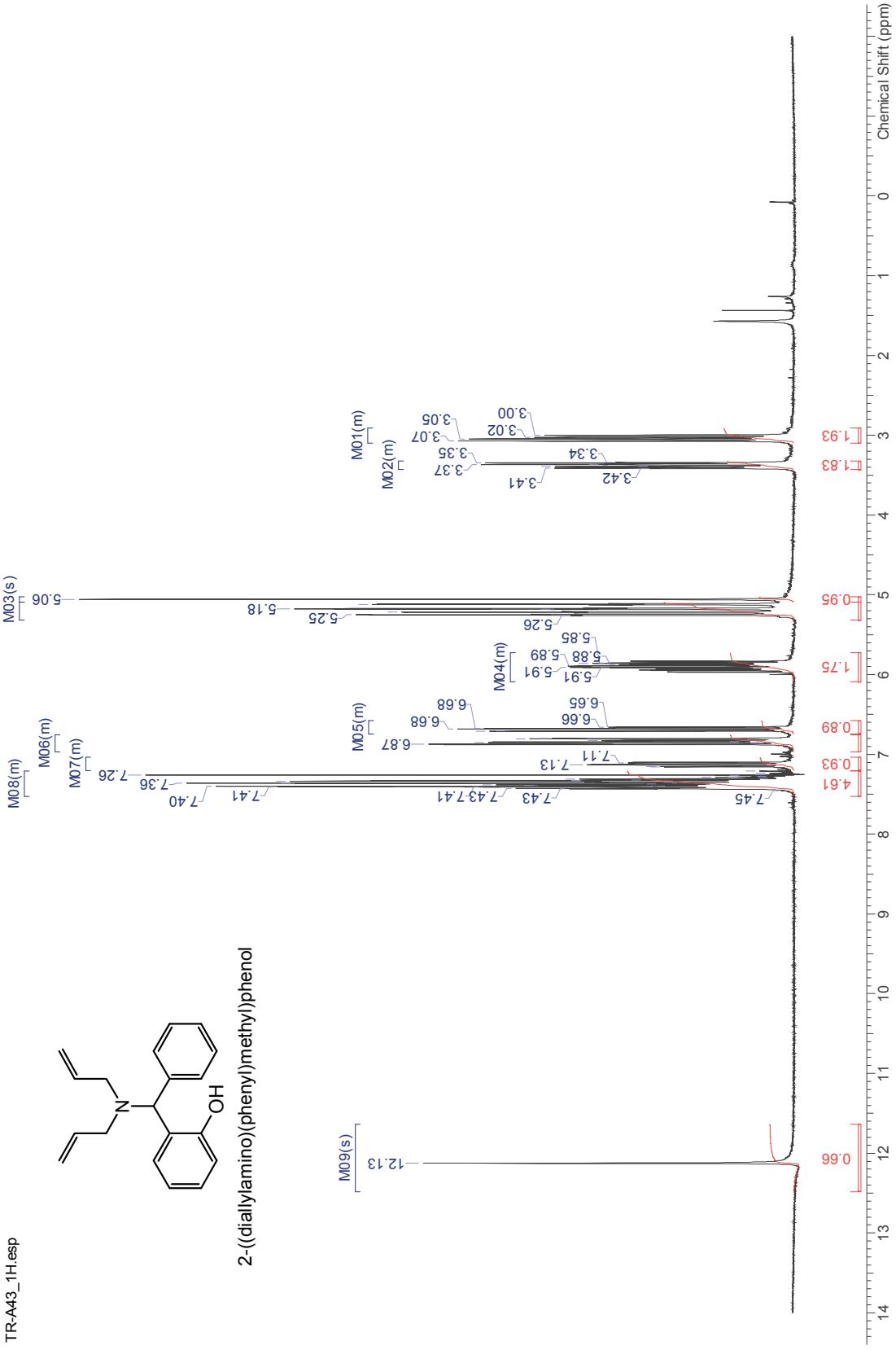
Appendix 13. ^{1}H NMR for compound 172



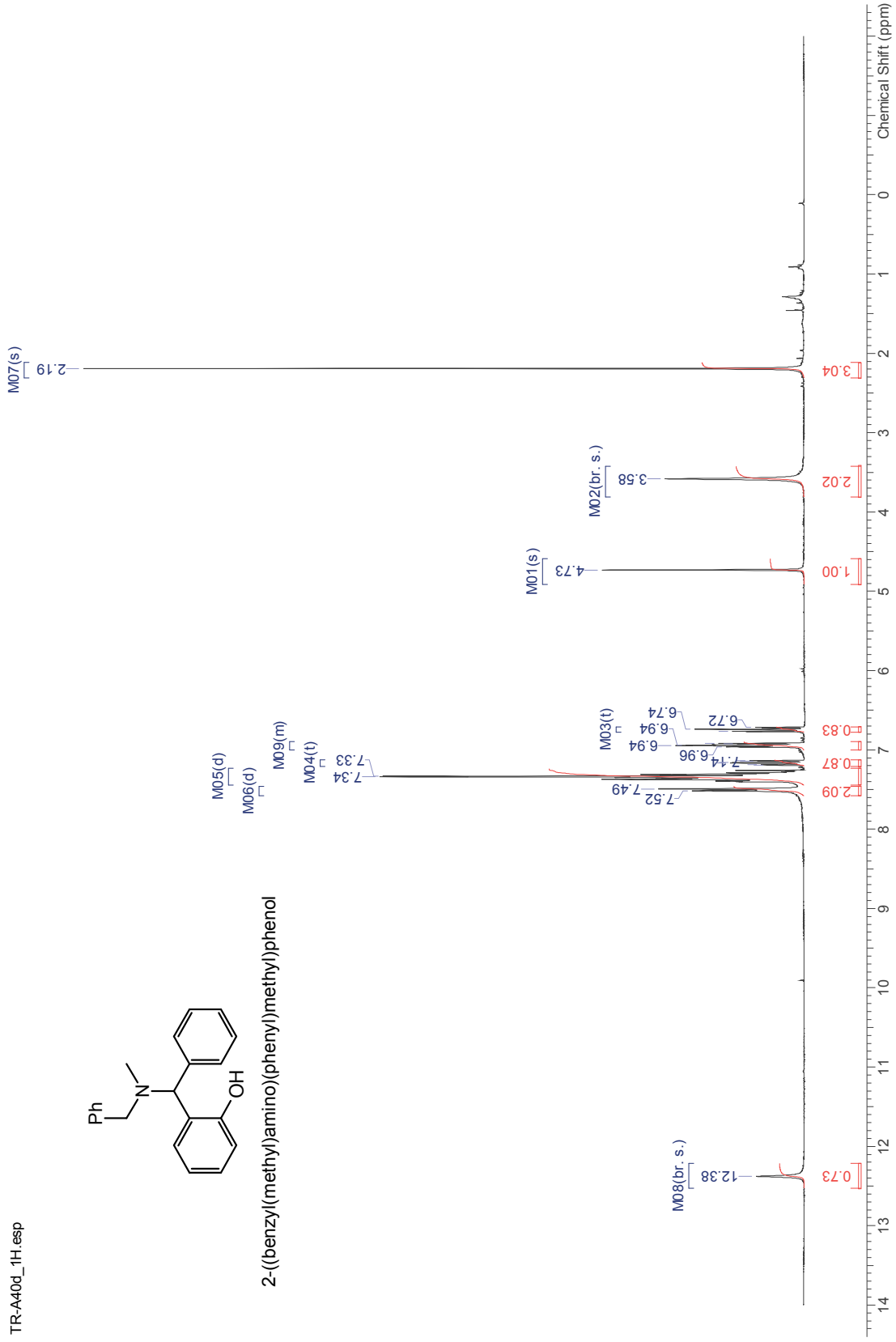
Appendix 14. ^{1}H NMR for compound 173



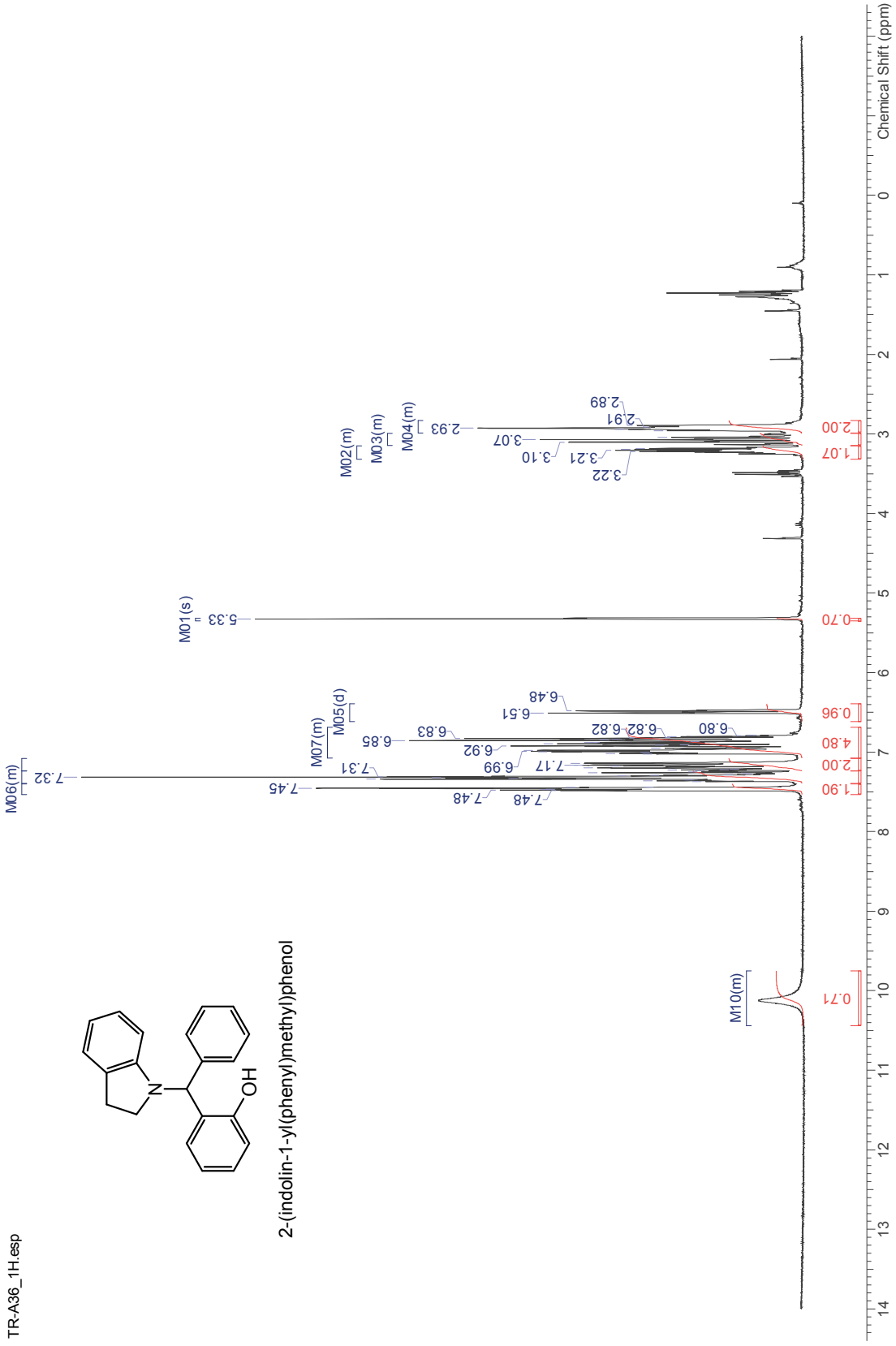
Appendix 15. ^{1}H NMR for compound 175



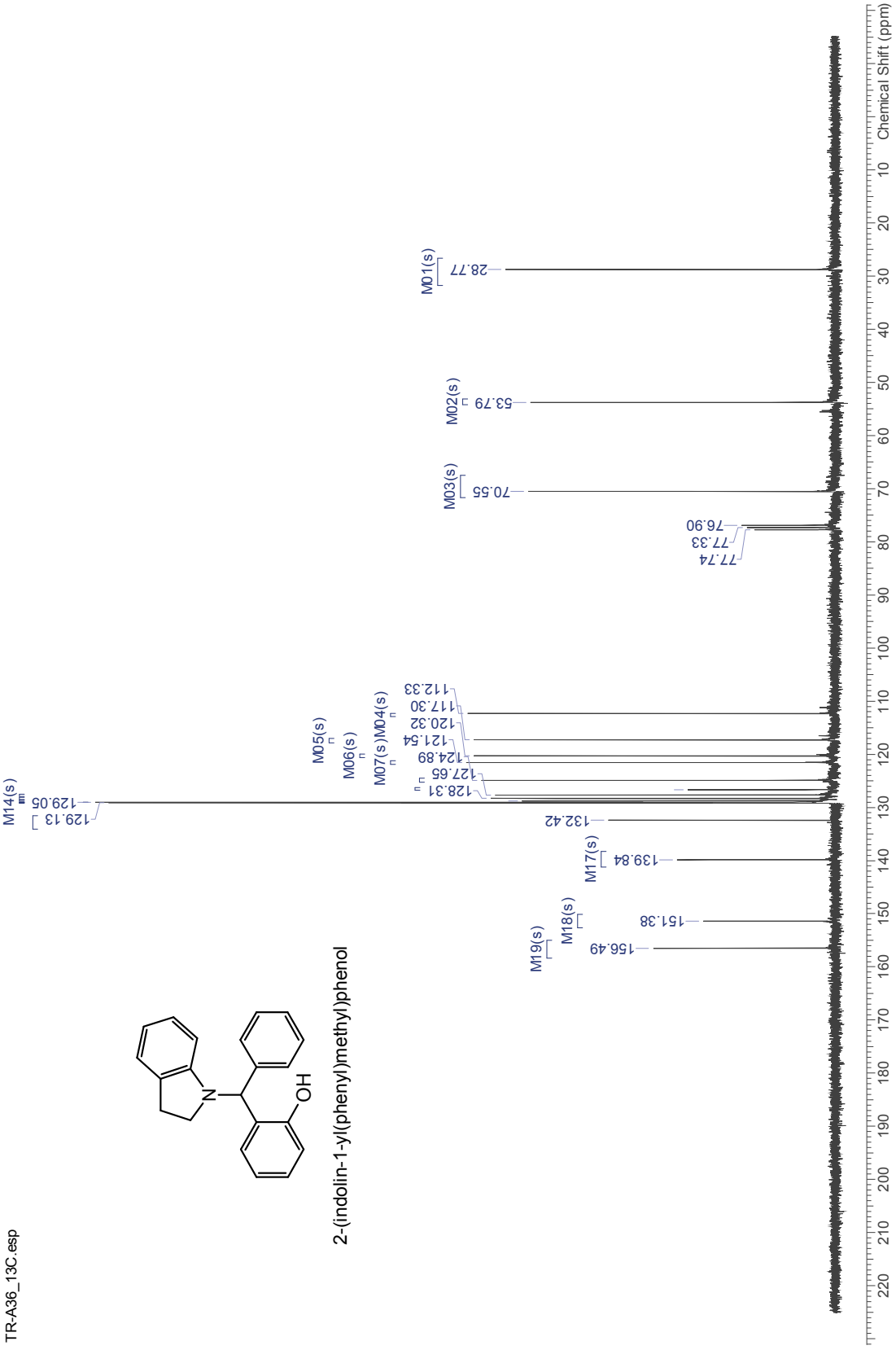
Appendix 16. ^{1}H NMR for compound 177



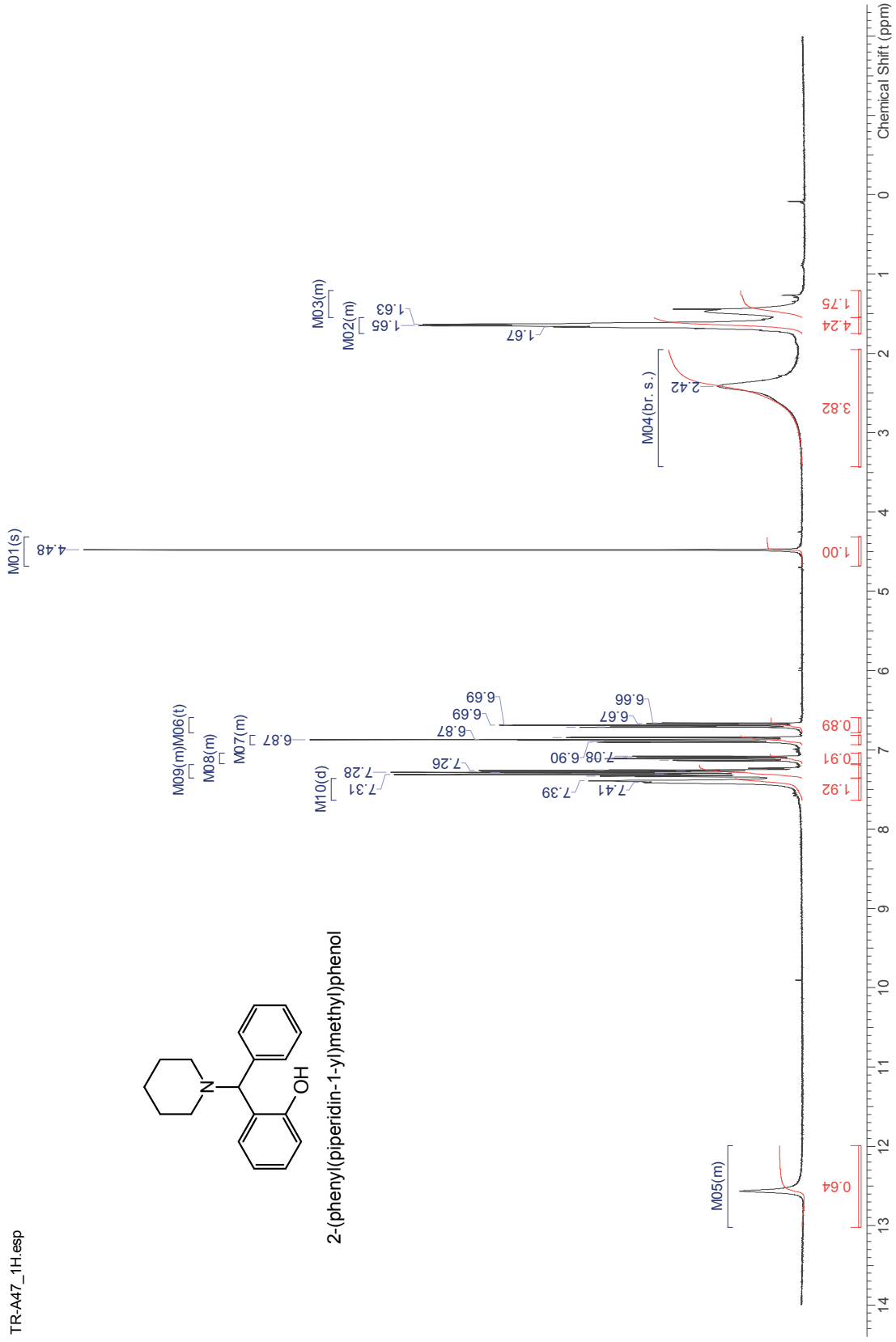
Appendix 17. ^{1}H NMR for compound 151



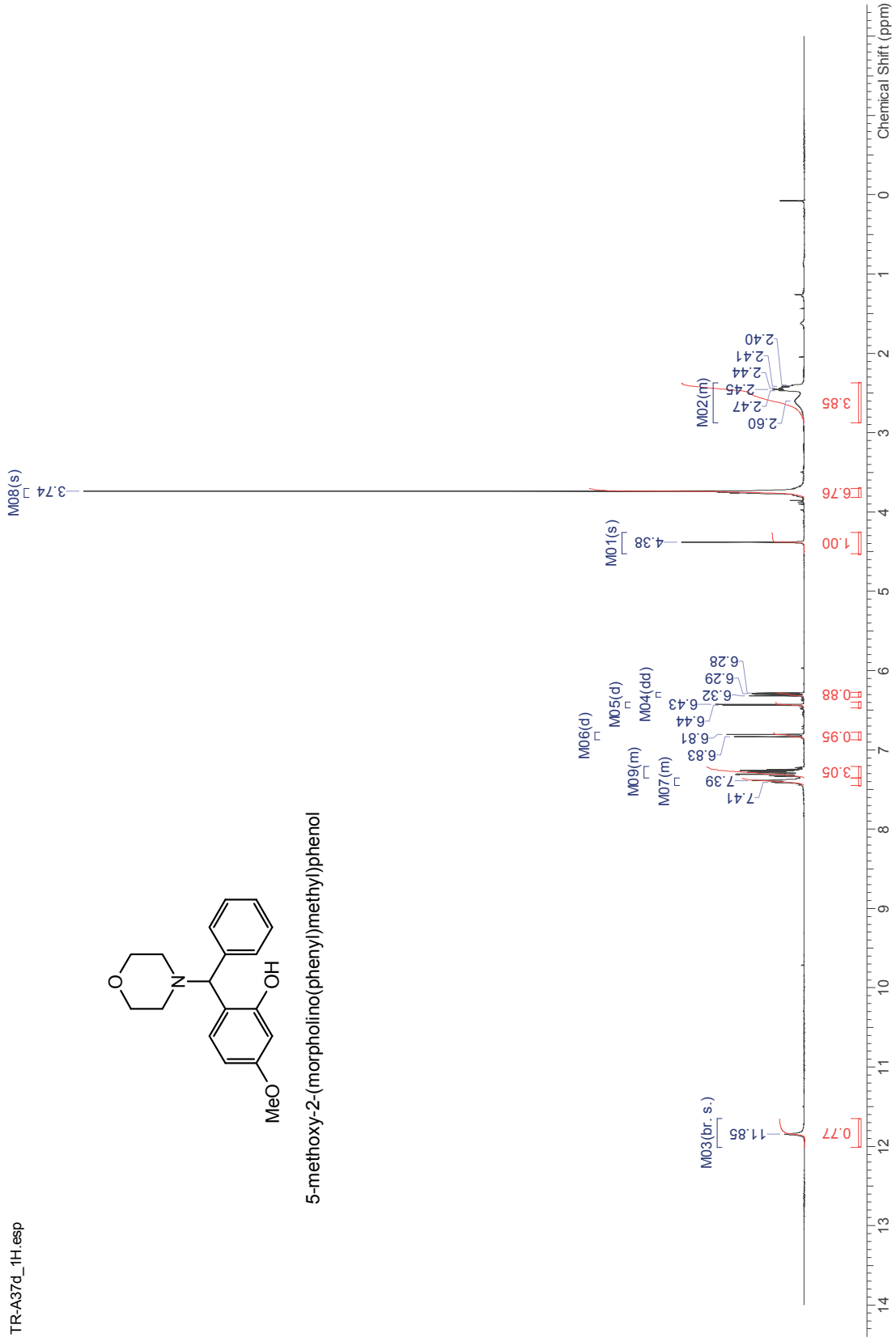
Appendix 18. ^{13}C NMR for compound 151



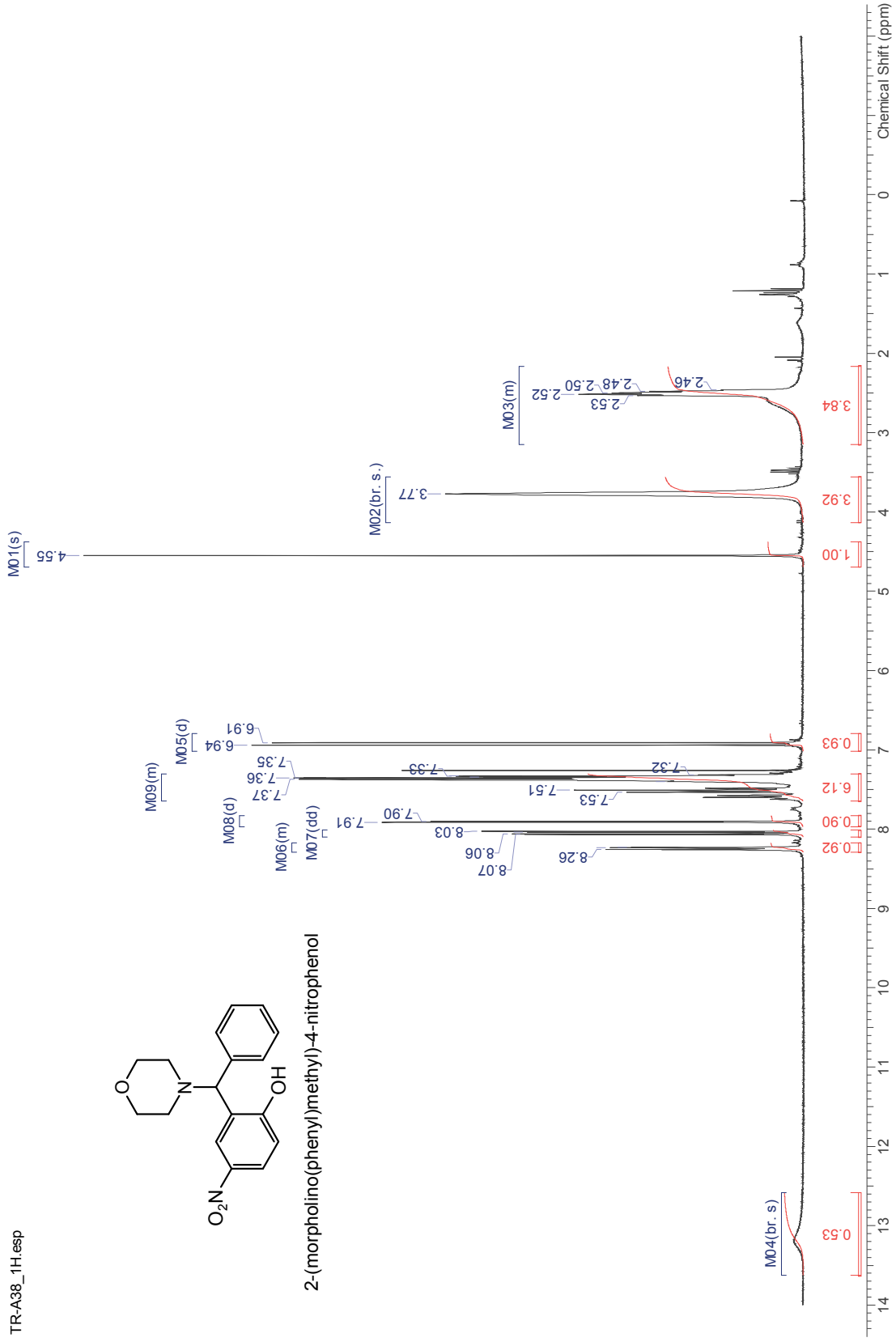
Appendix 19. ^{1}H NMR for compound 178



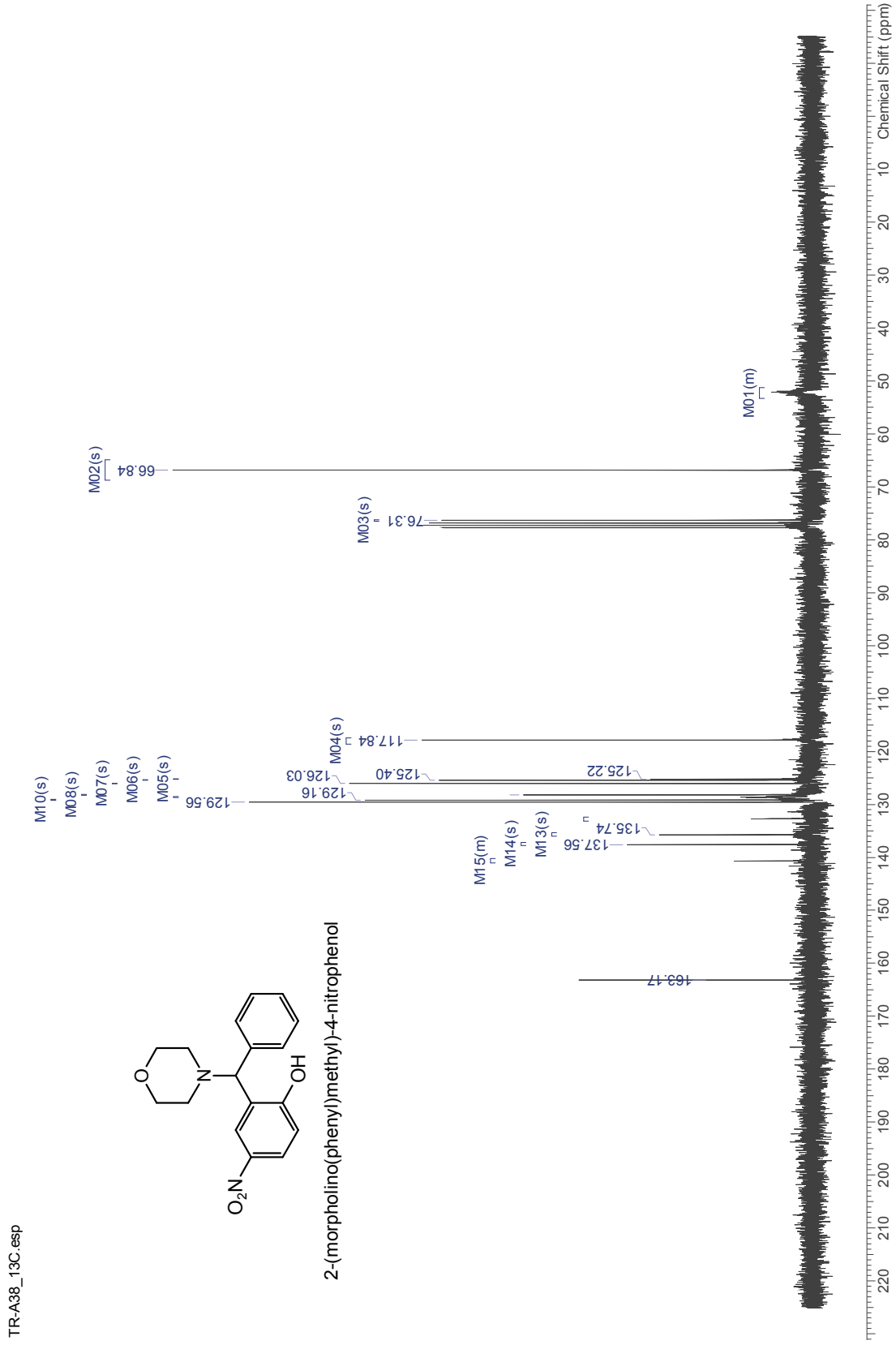
Appendix 20. ^{1}H NMR for compound 180



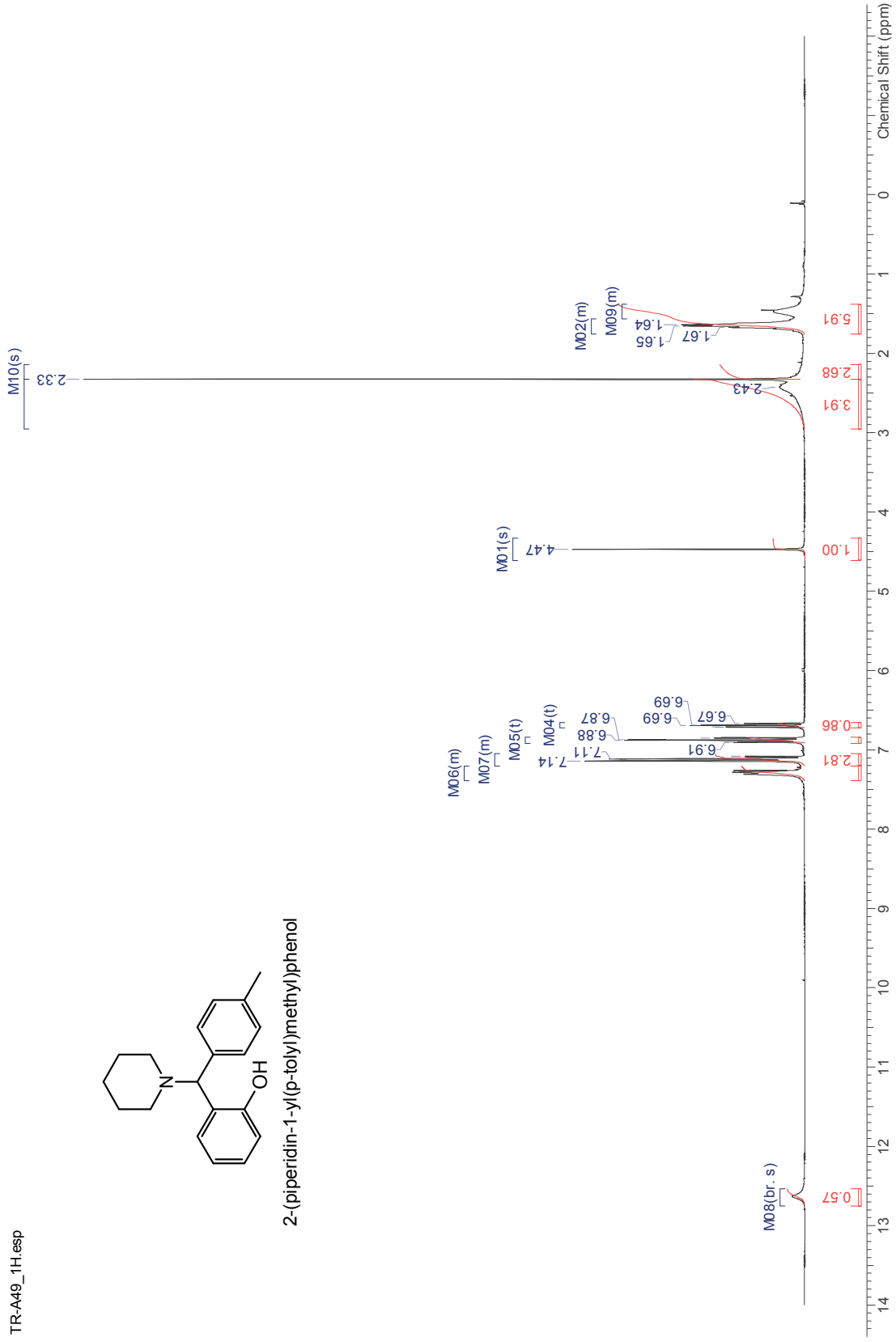
Appendix 21. ^{1}H NMR for compound 182



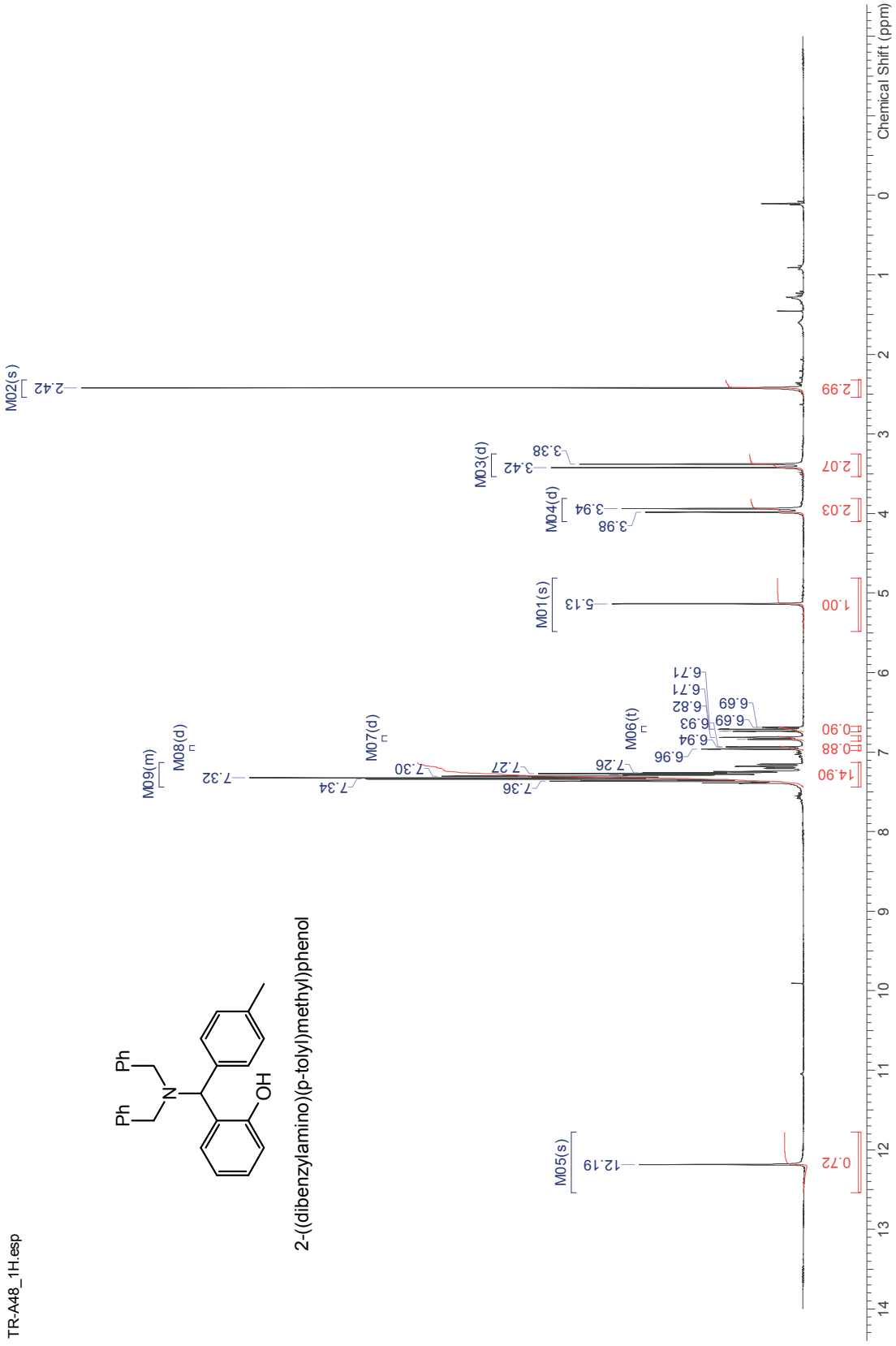
Appendix 22. ^{13}C NMR for compound 182



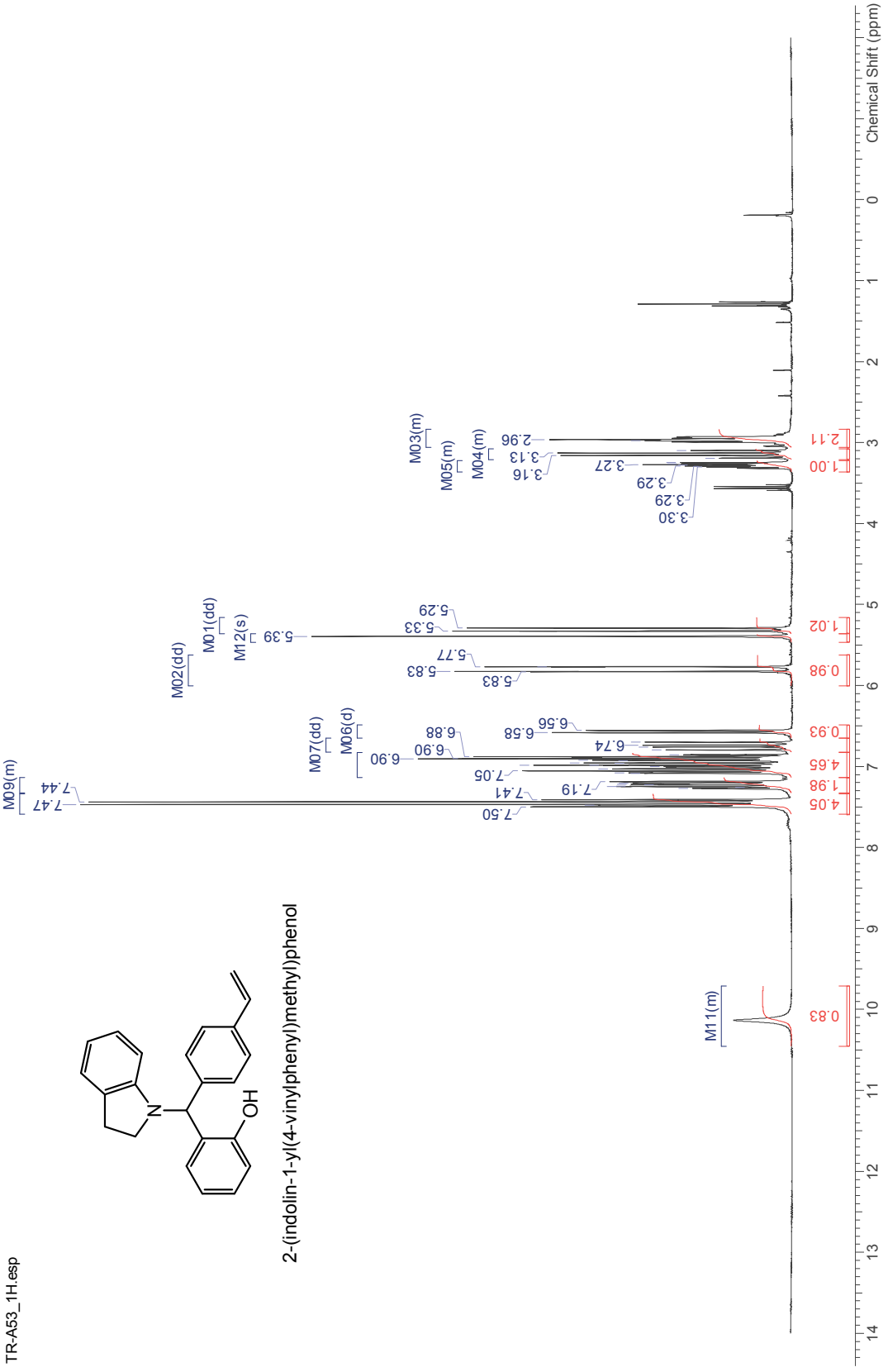
Appendix 23. ^{1}H NMR for compound 147



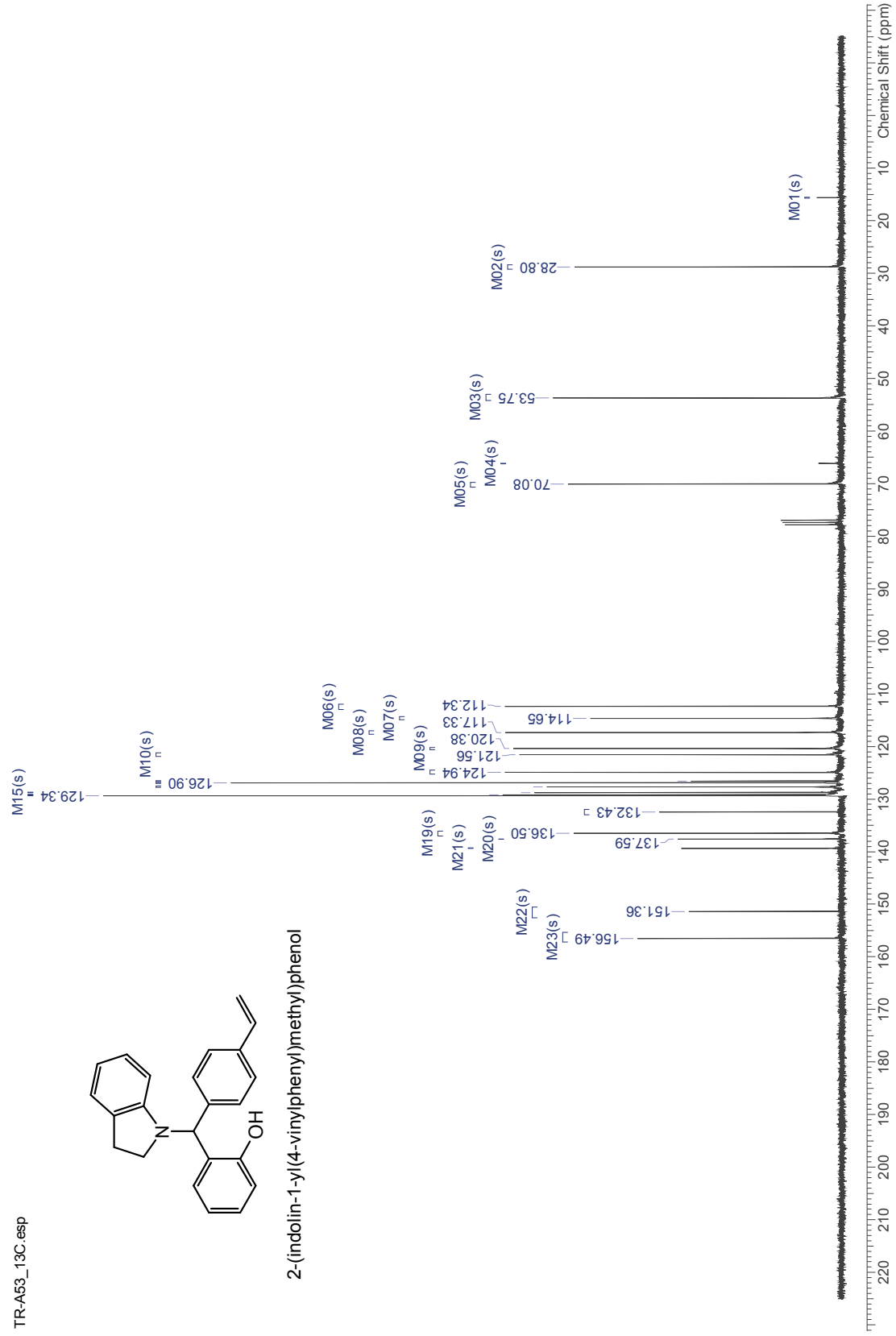
Appendix 24. ^{1}H NMR for compound 145



Appendix 25. ^{1}H NMR for compound 150



Appendix 26. ^{13}C NMR for compound 151



Appendix 27. ^{1}H NMR for compound 152